Editorial

La Revista Latinoamericana de Hipertension publica el tercer numero del volumen dos de 2007. Todos los articulos incluidos son de revision en el area de hipertension arterial resistente al tratamiento, sindrome metabolico, calcio e hipertension arterial, infeccion subclinica como causa de inflamacion en el embarazo y mecanismos endoteliales de la disfuncion endotelial.

Todos los articulos son escritos por investigadores reconocidos: Carlos Felstein de Argentina, Igor Morr de Venezuela, Ayrton Brandao de Brasil, Patricio Lopez Jaramillo de Colombia, Climaco Cano y Valmore Bermudez de Maracaibo.

Dr. Manuel Velasco

Dr. Rafael Hernández-Hernández

Editores en Jefe

Dra. María José Armas de Hernández

Editora Ejecutiva

Revista Latinoamericana de Hipertensión

INDIZADA EN:
1) LIVECS (Literatura Venezolana para la Ciencias de la Salud)

Sumario - Volumen 2, Nº 3, 2007

Volumen 2, Nº 3, 2007
Depósito Legal: PP200602DC2167
ISSN: 1856-4550

Sociedad Latinoamericana de Hipertensión
Dirección: Escuela de Medicina José María Vargas, Cátedra de Farmacología, piso 3. Esq. Pirineos. San José. Caracas-Venezuela. Telfs. 0212-5619871
E-mail: latinoamericanadehipertension@gmail.com

Comercialización y Producción:
Felipe Alberto Espino
Telefono: 0212-881.1907- 0416-811.6195 / 0414-2189431
e-mail: felipeespino7@gmail.com

Diseño de portada y diagramación:
Mayra Gabriela Espino
Telefono: 0412-922.25.68
e-mail: mayraespino@gmail.com

Alcance y Política Editorial

La Revista Latinoamericana de Hipertensión es una publicación biomédica periódica, arbitrada, de aparición trimestral, destinada a promover la productividad científica de la comunidad nacional e internacional en toda el área del Sistema Cardiovascular; la divulgación de artículos científicos y tecnológicos originales y artículos de revisión por invitación del Comité Editorial.

Está basada en la existencia de un Comité de Redacción, consistente en Editores en Jefe, Editores asociados y Comité Editorial. Los manuscritos que publica pueden ser de autores nacionales o extranjeros, residentes o no en Venezuela, en castellano o en ingles (los resumenes deben ser en ingles y castellano). Los manuscritos deben ser trabajos inéditos.

La Junta Directiva de la Revista no se hace responsable por los conceptos emitidos en los manuscritos. Los autores deben aceptar que sus manuscritos no se hayan sometidos o hayan publicados en otra revista. El manuscrito debe ir acompañado de una carta solicitud firmada por el autor principal y el resto de los autores responsables del mismo.

Forma de Preparación de los Manuscritos

Para la publicación de trabajos científicos en la Revista Latinoamericana de Hipertensión, los mismos estarán de acuerdo con los requisitos originales para su publicación en Revistas Biomédicas, según el Comité Internacional de Editores de Revistas Biomédicas (Arch. Intern. Med. 2006:126(36):1-47), www.icmje.com. Además, los editores asumen que los autores de los artículos conocen y han aplicado en sus estudios la ética de experimentación (Declaración de Helsinki). A tales efectos, los manuscritos deben seguir las instrucciones siguientes:

1. Mecanografiar original a doble espacio en idioma español, papel bond blanco, 216 x 279 mm (tamaño carta) con márgenes por lo menos de 25 mm, en una sola cara del papel. Usar doble espacio en todo el original. Su longitud no debe exceder las 10 páginas, excluyendo el espacio destinado a figuras y leyendas (4-5) y tablas (4-5).

2. Cada uno de los componentes del original deberán comenzar en página aparte, en la secuencia siguiente:
a. Página del título.
b. Resumen y palabras claves.
c. Texto.
d. Agradecimientos.
e. Referencias.
f. Tablas: cada una de las tablas en páginas apartes, completas, con título y llamadas al pie de la tabla.
g. Para la leyenda de las ilustraciones: use una hoja de papel distinta para comenzar cada sección. Enumere las páginas correlativamente empezando por el título. El número de la página deberá colocarse en el ángulo superior izquierdo de la misma.

3. La página del título deberá contener:
3.1. Título del artículo, conciso pero informativo.
a. Corto encabezamiento de página, no mayor de cuarenta caracteres (contando letras y espacios) como pie de página, en la página del título con su respectiva identificación.
b. Primer nombre de pila, segundo nombre de pila y apellido (con una llamada para identificar al pie de página el más alto grado académico que ostenta y lugar actual donde desempeña sus tareas el(los) autores.
c. El nombre del departamento (s) o instituciones a quienes se les atribuye el trabajo.
d. Nombre y dirección electrónica del autor a quien se le puede solicitar separatas o aclaratorias en relación con el manuscrito.
e. La fuente que ha permitido auspiciar con ayuda económica: equipos, medicamentos o todo el conjunto.
f. Debe colocarse la fecha en la cual fue consignado el manuscrito para la publicación.

4. La segunda página contiene un resumen en español y su versión en inglés, cada uno de los cuales tendrá un máximo de 150 palabras. En ambos textos se condensan: propósitos de la investigación, estudio, método empleado, resultados (datos específicos, significados estadísticos si fuese posible) y conclusiones. Favor hacer énfasis en los aspectos nuevos e importantes del estudio o de las observaciones. Inmediatamente después del resumen, proporcionar o identificar como tales: 3-10 palabras claves o frases cortas que ayuden a los indexadores en la construcción de índices cruzados de su artículo y que puedan publicarse con el resumen, utilice los términos del encabezamiento temático (Medical Subject Heading) del Index Medicus, cuando sea posible.

5. En cuanto al texto, generalmente debe dividirse en: introducción, materiales y métodos, resultados y discusión.

6. Agradecimientos, sólo a las personas que han hecho contribuciones reales al estudio.

7. Las referencias bibliográficas serán individualizadas por números arábicos, ordenados según su aparición en el texto. La lista de referencias bibliográficas llevarán por título "Referencias Bibliográficas" y su ordenamiento será según su orden de aparición en el texto.

Las citas de los trabajos consultados seguirán los requisitos de uniformidad para manuscritos presentados a revistas Biomédicas, versión publicada en: Ann Intern Med. 2006; 126(36): 1-47, www.icmje.com. No se aceptarán trabajos que no se ajusten a las normas.

8. Tablas: En hoja aparte cada tabla, mecanografiada a doble espacio; no presentar tablas fotográficas; enumere las tablas correlativamente y proporcione un título breve para cada una; dé a cada columna un encabezamiento corto o abreviado; coloque material explicativo en notas al pie de la tabla y no en el encabezamiento; explique en notas al pie de la tabla las abreviaturas no estandarizadas usadas en cada tabla; identifique claramente las medidas estadísticas de las variables tales como desviación estándar y error estándar de la medida; no use líneas horizontales ni verticales: citar cada tabla en orden correlativo dentro del texto; citar la fuente de información al pie de la tabla si ésta no es original.

9. Ilustraciones: Deben ser de buena calidad; entregarlas separadas; las fotos, en papel brillante con fondo blanco, generalmente 9 x 12 cm. Las fotografías de especímenes anatómicos, o las de lesiones o de personas, deberán tener suficiente nitidez como para identificar claramente todos los detalles importantes. En caso de tratarse de fotos en colores, los gastos de su impresión correrán a cargo del autor(s) del trabajo. Lo mismo sucederá con las figuras que superen el número de cuatro.

Todas las figuras deberán llevar un rótulo engomado en el reverso y en la parte superior de la ilustración indicando número de la figura, apellidos y nombres de los autores. No escribir en la parte posterior de la figura. Si usa fotografía de personas, trate de que ésta no sea identificable o acompañarla de autorización escrita de la misma. Las leyendas de las ilustraciones deben ser mecanografiadas a doble espacio en página aparte y usar el número que corresponde a cada ilustración. Cuando se usen símbolos y fechas, números o letras para identificar partes en las ilustraciones, identifíquelas y explíquelas claramente cada una en la leyenda. Si se trata de microfotografía, explique la escala e identifique el método de coloración.

10. Envíe un original y dos copias impresas en un sobre de papel grueso, incluyendo copias fotográficas y figuras entre cartones para evitar que se doblen, simultáneamente envíe una versión electrónica en disquete, indicando el programa de archivo. Las fotografías deben venir en sobre aparte. Los originales deben acompañarse de una carta de presentación del autor en la que se responsabiliza de la correspondencia en relación a los originales. En ella debe declarar que conoce los originales y han sido aprobados por todos los autores; el tipo de artículo presentado, información sobre la no publicación anterior en otra revista, congresos donde ha sido presentado y si se ha usado como trabajo de ascenso.

Acuerdo de asumir los costos de su impresión en caso de fotos a color, autorización para reproducir el material ya publicado o ilustraciones que identifiquen a personas.

11. Los artículos a publicarse, pueden ser: originales, revisiones, casos clínicos, y cartas al editor.

12. Cuando se refiere a originales, queda entendido que no se enviará artículo sobre un trabajo que haya sido publicado o que haya sido aceptado para su publicación en alguna parte.

13. Todos los trabajos serán consultados por lo menos por dos árbitros en la especialidad respectiva.

14. La Revista Latinoamericana de Hipertensión, no se hace solidaria con las opiniones personales expresadas por los autores en sus trabajos, ni se responsabiliza por el estado en el que está redactado cada texto.

15. Todos los aspectos no previstos por el presente reglamento serán resueltos por el Comité Editorial de la Revista.

16. La revista apoya las políticas para registro de ensayos clínicos de la Organización Mundial de la Salud (OMS) y del International Committee of Medical Journall Editors (ICMJE), reconociendo la importancia de esas iniciativas pera el registro y divulgación internacional de Información sobre estudios clínicos, en acceso abierto. En consecuencia, solamente se aceptarán para publicación, a partir de 2007, los artículos de investigaciones clínicas que hayan recibido un número de identificación en uno de los Registros de Ensayo Clínicos validados por los criterios establecidos por OMS e ICMJE, cuyas direcciones están disponibles en el sitio del ICMJE. El número de Identificación se deberá registrar al final del resumen.

Hipertensión arterial resistente al tratamiento

Antonio Olivieri, Maia Akopian, Ximena Manglano, Carlos A. Feldstein
Autor para correspondencia: Carlos A Feldstein (Director del Programa Hipertensión Arterial,
Hospital de Clinicas José de San Martín, UBA
Av. Córdoba 2351, 7º Piso (1120) Buenos Aires, Argentina
e-mail: carlfel@yahoo.com

Recibido: 14/04/2007 *Aceptado: 29/06/2007*

Resumen

La hipertensión resistente es una condición poco frecuente en la actualidad, aunque su incidencia no se conoce con precisión, en que la PA casual en consultorio permanece en niveles ≥ 140/90 mm Hg a pesar de la administración regular de tres drogas antihipertensivas incluyendo un diurético, en dosis adecuadas para el paciente- El diagnóstico requiere estudios para descartar causas secundarias de HTA, reconocer si hay falta de adherencia al tratamiento, exceso de consumo de sal, presencia de comorbilidades como diabetes mellitus, insuficiencia renal crónica, sobrepeso-obesidad, trastornos psicológicos como crisis de pánico, ansiedad y depresión. La presencia de daño de órganos blanco requiere un tratamiento más agresivo no farmacológico y farmacológico de la HTA, con el fin de controlar esta condición y prevenir el exceso de morbimortalidad que ocasiona.

Palabras clave: hipertensión resistente al tratamiento

Summary

Resistant hypertension is currently an unusual condition, even though it precisely incidence is not know, in which casual blood pressure measure at office remains ≥ 140/90 mmHg despite the regular administration of three antihypertensives drugs including a diuretic, in appropriate doses for the patient. The diagnosis requires some tests to rule out secondary causes of hypertension, recognize if there is a lack of adherence to treatment, excessive salt intake, presence of comorbidities such as diabetes mellitus, chronic renal disease, overweight-obesity, psychological disorders such as panic attack, anxiety and depression. The presence of target organ damage requires a more aggressive non pharmacologic and pharmacologic treatment of the hypertension, with the aim to control this condition and prevent the excess morbimortality it produces.

Key words: resistant hypertension, diagnosis and management

Introducción

El JNC VII define la hipertensión arterial (HTA) resistente o refractaria al tratamiento como niveles de presión arterial (PA) iguales o superiores a 140/90 mmHg, o a 130/80 mm Hg en pacientes con diabetes mellitus o enfermedad renal crónica (creatinina > 1,5 mg/dl o proteinuria >300 mg/24 hs.) a pesar de cumplir el tratamiento con dosis plenas de 3 fármacos antihipertensivos o más, incluyendo un diurético[1]. Los criterios de diagnóstico de la hipertensión resistente enunciados por la European Society of Hypertension/European Society of Cardiology (ESH/ESC) son la falta de control con "por lo menos 3 drogas", pero no especifican que una de ellas deba ser un diurético[2]. Otra categoría diagnóstica es la HTA de difícil control, que se define como niveles persistentemente elevados de PA a pesar del tratamiento con dos o tres drogas pero en que no se descartan la medicación insuficiente y la pobre adherencia y por ende, no cumple con los criterios estrictos antes mencionados para la

hipertensión resistente. La incidencia de la HTA de difícil control es mucho mayor que la de hipertensión resistente. Ambas condiciones son más frecuentes en pacientes de más de 60 años de edad[3]. La hipertensión resistente se presenta con relativamente baja frecuencia en la actualidad, debido a la evolución de las técnicas de diagnóstico y al empleo de las modernas familias de fármacos antihipertensivos disponibles. En estudios realizados en los ´80 se ha informado una prevalencia de hipertensión resistente que varía entre el 1% al 20% de los pacientes atendidos en servicios hospitalarios especializados en HTA[4,5]. Una reciente evaluación[6] comprobó que la prevalencia de hipertensión resistente se halla entre 2% - 5% de todos los hipertensos, siendo mas frecuente entre aquellos con daño de órganos blanco.

Los grandes ensayos clínicos han mostrado que las elevaciones de la PA diastólica resultan mas fáciles de controlar que las de la PA sistólica. En el ALLHAT después de 5 años de seguimiento 92% de los pacientes tuvieron niveles de PA diastólica <90 mm Hg mientras que 67% tuvieron niveles de PA sistólica <140 mm Hg[7]. Una mejor estimación de la prevalencia de hipertensión resistente se obtiene por los estudios de evolución en que el protocolo impone el tipo de droga a seleccionar y su dosis. En este aspecto, analizando los resultados del Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[8] que incluyó mas de 33.000 pacientes con un promedio de seguimiento de aproximadamente 5 años, Epstein[9] postuló que sumando el número de pacientes en quienes la PA se mantuvo elevada aun recibiendo tres agentes antihipertensivos al 8% que recibió 4 o mas agentes antihipertensivos, resultaría un total de 15% de la cohorte que podría clasificarse como hipertensión resistente. En el estudio Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE)[10] efectuado en hipertensos de mas de 55 años con por lo menos 1 factor de riesgo cardiovascular además de la HTA, 33% permanecían con niveles de PA>140/90 mm Hg, y el 18% se hallaba tratado con 3 o mas agentes antihipertensivos cumpliendo los criterios de hipertensión resistente.

Dos condiciones que pueden confundirse con la hipertensión resistente son la falta de adherencia al tratamiento y la pseudorresistencia. La falta de adherencia al tratamiento es una causa frecuente de control inadecuado de la PA. Los ancianos por distintas razones como instrucción inadecuada suministrada por el médico o dificultad cognoscitiva para la comprensión de todo lo relacionado con la prescripción de varios fármacos, o ante la existencia de efectos colaterales de la medicación, o por razones económicas que les impiden acceder al tratamiento antihipertensivo adecuado constituyen la cohorte que con más frecuencia presenta hipertensión de difícil control o con una verdadera hipertensión resistente. La pseudorresistencia incluye a su vez entre sus causas a la HTA de guardapolvo blanco y a la pseudohipertensión. La hipertensión de guardapolvo blanco es una condición caracterizada por cifras elevadas de PA solo en el consultorio. Constituye una reacción de alerta que consiste en una respuesta hemodinámica a un incremento de la actividad del sistema nervioso simpático, ante estímulos ambientales que representan amenaza o estrés, con aumento agudo de la PA sistólica, la PA diastólica y de la frecuencia cardíaca. Este fenómeno puede durar minutos a horas, no se modifica significativamente con fármacos antihipertensivos, no depende de la PA basal y su magnitud es mayor para la PAS, en los hipertensos y en los ancianos (tal vez debido a la mayor variabilidad de la PA en esta población)[11]. Mancia y col[11] por medio del registro intraarterial continuo evaluaron los controles esfigmomanométricos realizados por el médico cada 15 minutos y observaron que el fenómeno de alerta se atenuaba parcialmente a los 10 minutos, y que era mucho menor si las mediciones de la PA eran efectuadas por una enfermera o con un equipo automático de registro. La PA en el consultorio puede aumentar un 20-30% con respecto a los valores basales, pero la prevalencia de hipertensión de guardapolvo blanco es de aproximadamente el 20% en algunas series[12]. La misma disminuye conforme aumenta la severidad de la HTA. Debe sospecharse en pacientes que presentan registros de PA normales en su domicilio y síntomas secundarios a hipotensión arterial al aumentar las dosis del tratamiento antihipertensivo, así como en aquellos hipertensos sin daño de órgano blanco (especialmente hipertrofia ventricular izquierda). La hipertensión de guardapolvo blanco acarrea el riesgo de someter a los pacientes a tratamientos innecesarios y puede resultar en un diagnóstico equivocado de hipertensión resistente. Garg y cols[13] comprobaron que un tercio de los pacientes con aparente hipertensión resistente tuvo niveles promedios de PA en el monitoreo ambulatorio de PA (MAPA) de 24 horas inferiores a 130/85 mm Hg. Muxfeldt y cols[14] sostuvieron que el monitoreo ambulatorio de PA (MAPA) es el único método no invasivo que permite diferenciar la "hipertensión resistente de consultorio" de la verdadera hipertensión resistente. Esos autores observaron que 69% de sus pacientes con hipertensión resistente presentaron comportamiento non-dipper[14], lo que adjudicaron por lo menos en parte a la ausencia de cobertura terapéutica homogénea durante las 24 horas en aquellos pacientes que solo recibieron medicaciones en la mañana[15].

La pseudohipertensión es una condición que puede sugerir falsamente la hipertensión resistente y que ocurre más comúnmente en pacientes con arteriosclerosis avanzada (ancianos, falla renal crónica progresiva, y en diabéticos) y que se debe a lesiones cal-

cificadas que confieren rigidez vascular marcada por lo que es muy difícil que el manguito inflado a alta presión comprima completamente las arterias humeral y radial. En esas condiciones, pueden palparse los latidos de dichas arterias distalmente al manguito inflado a niveles mas elevados a los que corresponde la verdadera PAS determinada en forma directa (intraarterial) (signo de Osler)[16]. Un estudio comparativo entre las determinaciones esfigmomanométricas e intraarteriales directas mostró que con las primeras la PA tuvo cifras entre 10 a 54 mmHg superiores a las obtenidas con las segundas[16]. En consecuencia, se sostuvo que la pseudohipertensión solo puede descartarse por cateterismo arterial. Puede sospecharse cuando en un anciano la comprobación de cifras elevadas de PAS no coexiste con daño de órganos blanco, cuando el tratamiento antihipertensivo induce síntomas de hipoperfusión sin reducción de la PA, y si se comprueba radiográficamente la calcificación de la arteria humeral[17]. La maniobra de Osler no resulta confiable para descartar la pseudohipertensión, pues puede ser positiva en hipertensos aun con manifestaciones de daño de órganos nobles, y también en ausencia de pseudohipertensión[18].

Las etiologías más frecuentes de hipertensión resistente se hallan en la Tabla 1.

Table 1. Causas de Hipertensión Resistente

1) Relacionadas con las drogas.
- *Dosis insuficientes.*
- *Combinaciones inapropiadas.*
- *Rápida inactivación (hidralazina).*
- *Interacción con otras drogas: corticoides, antiinflamatorios no esteroides (AINES), descongestivos nasales, simpaticomiméticos, antidepresivos, supresores del apetito, anticonceptivos orales, ciclosporina, tacrolimus, eritropoyetina, cocaína, hierbas (ginseng, yohimbina), esteroides anabólicos.*

2) Condiciones asociadas.
- *Sobrepeso-Obesidad.*
- *Tabaquismo.*
- *Excesiva ingesta de alcohol.*
- *Insuficiencia renal.*
- *Resistencia a la insulina.*
- *Dolor crónico.*
- *Trastornos de ansiedad-ataque de pánico.*
- *Intensa vasoconstricción (arteritis, fenómeno de Raynaud).*

3) Sobrecarga de volumen.
- *Inadecuada terapia con diuréticos.*
- *Exceso de ingesta de sal.*
- *Retención de fluidos secundaria a la disminución de la PA con antihipertensivos.*
- *Daño renal progresivo (nefroesclerosis).*

4) Hipertensión Secundaria

Relacionadas con las Drogas: la terapia farmacológica subóptima parece ser la causa más frecuente de hipertensión resistente, principalmente por la inadecuada administración de diuréticos que prevengan o corrijan la expansión de volumen[19,20]. A veces, los responsables de estas falencias son los propios médicos, que no intensifican la terapia antihipertensiva cuando no hay una adecuada respuesta al tratamiento[21]. Berlowitz y col.[22] en 800 hipertensos varones ancianos seguidos durante un periodo de 2 años comprobaron en aproximadamente 40% niveles iguales o superiores a 160/90 mm Hg a pesar de efectuar un promedio de 6 consultas médicas por año relacionadas al manejo de la HTA. Esos autores señalaron que una de las causas más importantes de la falta de control es un enfoque médico poco agresivo del tratamiento. Las interacciones medicamentosas pueden producir una disminución del efecto reductor de la PA por alterar la absorción, el metabolismo o la excreción de las drogas antihipertensivas (Tabla 2). En un estudio retrospectivo sobre las causas de hipertensión resistente, Garg y col.[13] en 58% de 141 pacientes señalaron su vinculación con las drogas utilizadas (interacciones medicamentosas, abandono del tratamiento por efectos colaterales, y tratamiento subóptimo) mientras que en 9% se relacionó con causas psicológicas; y en 5% con HTA secundaria (estenosis de la arteria renal, hiperaldosteronismo primario, feocromocitoma, hipertiroidismo, hiperparatiroidismo). Esos autores hallaron falta de adherencia al tratamiento en 16% de los pacientes y pseudorresistencia por HTA de guardapolvo blanco en 6%. Entre las drogas que pueden causar resistencia al tratamiento por distintos mecanismos podemos mencionar: aminas simpaticomiméticas, clorpromazina, colestiramina, sucralfato, antidepresivos tricíclicos, eritropoyetina, ciclosporina, cocaína, anfetaminas, corticoides y anticonceptivos orales (Tabla 2). La acción terapéutica de los IECA[23] y de los diuréticos de asa depende de la disponibilidad de estas prostaglandinas. El efecto de los calcioantagonistas es menos afectado por los AINES. La aspirina a 80 mg/día no interfiere con el efecto de las drogas antihipertensivas[24].

Table 2. Interacciones entre drogas que pueden causar HTA

Droga antihipertensiva	Droga que interactúa	Mecanismo de interacción
Hidroclorotiazida Furosemida	Colestiramina Sucralfato	Disminuyen la absorción
Propranolol	Rifampicina	Incrementa el metabolismo hepático
Inhibidores de Enzima Convertidora, β bloqueantes, Hidralazina, diuréticos	AINES	Disminuyen las prostaglandinas vasodilatadores renales, y aumentan la retención de sodio
Alfa-metildopa, clonidina	Naloxona	Disminuye la inhibición del sistema nervioso central y aumenta la actividad simpática
Todos las drogas antihipertensivas	Cocaína, antidepresivos tricíclicos	Disminuyen la recaptación de noradrenalina a nivel presináptico
Todos las drogas antihipertensivas	Fenilpropanolamina y otros simpaticomiméticos	Estimulación directa del receptor adrenérgico

Condiciones Asociadas: existen controversias respecto a la relación entre trastornos psicológicos e hipertensión resistente. Davies y cols[25] en un estudio caso-control comparando pacientes con hipertensión resistente y pacientes con HTA bien controlada no hallaron diferencias en la prevalencia de ataques de pánico, ansiedad y depresión entre ambos grupos. Sin embargo, comprobaron que las crisis de pánico tuvieron una prevalencia remarcablemente alta en ambos grupos (33% y 39%, respectivamente). Kaplan[26] halló hiperventilación inducida por ansiedad en 96 de 300 pacientes evaluados. En otro estudio, Davies y cols[27] señalaron que la intolerancia medicamentosa por efectos adversos inespecíficos en pacientes hipertensos se relacionó con ataques de pánico y otras manifestaciones de morbilidad psiquiátrica.

Otro grupo con alta incidencia de hipertensión resistente son los hipertensos diabéticos[28]. Por otra parte, se ha señalado que en pacientes de escasos recursos económicos la HTA severa pobremente controlada se relaciona con la falta de controles médicos, de cumplimiento del tratamiento farmacológico y del abuso de ingesta crónica de bebidas alcohólicas[29]. La relación directa entre la cantidad de alcohol consumido y la PA constituye una de las asociaciones más fuertes potencialmente modificables como factor de riesgo de HTA[30]. Un "trago" estándar es usualmente definido como 14 g de alcohol (etanol). Esa cantidad se halla presente en 12 onzas (350 ml) de cerveza, 5 onzas (145 ml) de vino, o 1,5 onzas (45 ml) de bebidas espirituosas destiladas al 40%. Cuanto mayor es el consumo de alcohol por encima de 2 tragos diarios, más alta es la PA. El consumo habitual de alcohol (etanol) en cantidades superiores a 30 ml (1 onza) diarios produce también elevación de la PA[31]. En estudios prospectivos observacionales (32) se comprobó que la PA disminuye a los pocos días al reducir o suprimir la ingesta de bebidas alcohólicas. Al menos se han efectuado 12 estudios randomizados para examinar el efecto de la reducción en el consumo de alcohol sobre la PA[33]. Henningsen y col.[34] comprobaron que la ingesta de bebidas alcohólicas se asocia con resistencia al tratamiento antihipertensivo. Aún cuando la aparente resistencia puede deberse a la pobre o a la escasa adherencia a la medicación antihipertensiva en los consumidores crónicos de altas cantidades de bebidas alcohólicas, puede haber también una interferencia del etanol con los efectos reductores de la PA de aquellos agentes[33]. El tabaquismo eleva la PA y la frecuencia cardíaca en forma aguda, y aunque no es una causa de HTA, reduce el efecto de las drogas antihipertensivas y es un factor de riesgo mayor de enfermedades cardiovasculares, por lo que debe intentarse enfáticamente su supresión[35]. Los niveles de propranolol disminuyen aproximadamente un 37% en los fumadores, posiblemente por aumentar su metabolismo, al ser estimulado el citocromo P450.

La sobrecarga de volumen es frecuente en los pacientes con hipertensión resistente. La exagerada ingesta de sodio, la insuficiencia renal subyacente y la retención reactiva de sodio que se produce con el uso de algunas clases de fármacos antihipertensivos no diuréticos, como los beta-bloqueantes, los bloqueantes alfa- y beta-adrenérgicos, y los vasodilatadores directos aumenta el volumen plasmático, y disminuye o anula el efecto de los fármacos antihipertensivos. Los calcioantagonistas, los inhibidores de enzima convertidora (IECAs) y los bloqueantes de los receptores de angiotensina II –BRAs- no producen retención hídrica. La comprobación de que la HTA es hiporreninémica, no obstante, no resulta predictiva de un exceso de volumen. La ingesta excesiva de sal disminuye el balance negativo de sodio y agua y contrarresta la acción de los diuréticos. Esta es una situación muy frecuente y puede contribuir a la hipertensión resistente. Una natriuria diaria mayor a 100 - 120 mEq sugiere fuertemente un consumo excesivo de sal. La sensibilidad a la sal está aumentada en los pacientes que tienen más de 60 años de edad, en los que presentan daño renal, en los negros y en los obesos. La obesidad, particularmente abdominal o central, habitualmente se asocia a HTA relacionada a un estado de hiperinsulinemia secundario a resistencia a la insulina. Más del 40% de los pacientes con hipertensión resistente son obesos[36], y éstos pueden requerir un tratamiento más agresivo con fármacos antihipertensivos.

Hipertensión arterial secundaria: los indicios clínicos que sugieren una causa secundaria de la HTA se hallan en la Tabla 3.

Tabla 3. Indicadores clínicos de una posible causa de HTA secundaria

1. Inicio antes de los 20 años de edad o después de los 50
2. Enfermedad renal crónica
3. Detección por estudios de imágenes de riñones "pequeños"
4. Soplo sistodiastólico en epigastrio o flancos (estenosis de la arteria renal)
5. Palpación de ambos riñones aumentados de tamaño (poliquistosis renal)
6. Estrías purpúricas, cara de "luna llena", "jiba de búfalo" (enfermedad de Cushing)
7. Crisis hipertensiva paroxística, palpitaciones, cefalea, precordialgia, sudoración, temblor (feocromocitoma).
8. Estigmas cutáneos de neurofibromatosis de von Recklinghausen (feocromocitoma)
9. Hipokalemia no atribuible a diuréticos, astenia, poliuria, polidipsia, calambres y debilidad muscular, parestesias (hiperaldosteronismo primario)
10. PA en miembros inferiores menores a las de brazos; disminución y retardo de los pulsos en miembros inferiores (coartación de aorta)
11. HTA moderada a severa con asimetría del tamaño renal
12. Alteraciones del sueño, ronquidos, somnolencia diurna, obesidad central (apnea del sueño)
13. Daño de órgano blanco
14. HTA acelerada o maligna (retinopatía grado III-IV)
15. Súbita peoría de la HTA a cualquier edad
16. HTA con elevación reciente e inexplicable de la creatininemia al administrar un inhibidor de la enzima de conversión de la angiotensina (IECA) (HTA por estenosis de arterias renales)
17. HTA resistente al tratamiento

Debe sospecharse una causa secundaria en todo paciente con HTA catalogada como esencial en quien en forma rápida se instala una falta de efectividad del régimen antihipertensivo con el que previamente se controlaba adecuadamente las cifras tensionales[37]. La HTA es con frecuencia no controlada hasta que se trata adecuadamente la causa que la provoca[38]. Anderson y cols[39] evaluaron en un período de 18 años 4.000 pacientes con hipertensión resistente, hallando HTA secundaria en 10% de los pacientes en general, y en 17% los mayores de 60 años. La apnea obstructiva del sueño está claramente relacionada con la HTA, sobretodo en pacientes con hipertensión resistente. Logan y cols[40] diagnosticaron apnea obstructiva del sueño previamente no sospechada en 34 de 41 individuos con hipertensión resistente. La prevalencia de hipertensión resistente es mayor en los que sufren apnea obstructiva del sueño con un índice mas elevado de alteración respiratoria, en comparación con aquellos con HTA más fácilmente controlada[41]. La hipoxemia e hipercapnia incrementan el tono simpático mediante la estimulación de los quimiorreceptores centrales y periféricos. Asimismo, durante la apnea no se estimulan los receptores pulmonares de estiramiento que normalmente regulan y suprimen la descarga simpática. Así, el tono simpático se incrementa, inicialmente de noche y en forma transitoria, pero con el tiempo lo hace en forma permanente, produciendo HTA[42]. También está aumentada la excreción de catecolaminas[43], endotelina-1[44], eritropoyetina[45], y de aldosterona[46]. El tratamiento de la apnea obstructiva del sueño con presión positiva continua en vías aéreas (CPAP) mejora el control de la PA[47] y disminuye la actividad simpática en los músculos.

En la Figura 1 se resume un enfoque que sugerimos para la evaluación y seguimiento de los pacientes con hipertensión resistente. El JNC-VII enfatiza la necesidad de evaluar, como causa posible de hipertensión resistente, las HTA secundarias. Se deberá solicitar el laboratorio de rutina, incluyendo el hematocrito, hemoglobina, ionograma sérico, glucemia, clearance de creatinina o por lo menos cálculo de la filtración glomerular por la ecuación Modification of Diet in Renal Disease (MDRD)[48] o en su defecto por la de Cockcroft-Gault[49], perfil lipídico (colesterol total, colesterol-HDL, y triglicéridemia), orina completa con sedimento, y electrocardiograma. Las posibles causas secundarias serán investigadas en base al cuadro clínico de cada paciente en particular, siguiendo los protocolos correspondientes[19]. El MAPA puede ser utilizado para distinguir entre la hipertensión resistente y la hipertensión de guardapolvo blanco. Brown y col[50] encontraron que 20%-30% de pacientes con aparente hipertensión resistente presentaban PA normal en el MAPA, por lo que considerando el elevado costo de los estudios y tratamientos de las causas secundarias de HTA, estiman que la evaluación del perfil circadiano de la PA estaría indicada para iniciar el estudio de los pacientes con aparente hipertensión resistente. Se debe insistir enfáticamente a los pacientes que cumplan la dieta hiposódica, reduzcan su peso corporal en caso de sobrepeso u obesidad, realicen ejercicios aeróbicos y reduzcan la ingesta de alcohol en los casos de abuso. Corresponde explicar a los pacientes que el 75% de la sal que incorporan a su organismo está presente en los alimentos manufacturados; sólo el 25% de la sal que ingieren es la del "salero de mesa". Se puede mejorar la adherencia al tratamiento citando regularmente al paciente al consultorio, incluso recordándole las consultas por vía telefónica. El empleo de la asociación de dos drogas en un mismo comprimido puede mejorar también la adherencia y aún hacer más económica la terapia. La frecuencia cardíaca elevada puede ocasionalmente sugerir la presencia de sobrecarga de volumen e hiperactividad simpática[51]. Como la sobrecarga de volumen es frecuente entre los pacientes con hipertensión resistente conviene agregar diuréticos al tratamiento o incrementar su dosis ya que más del 60% van a responder a esta estrategia[52]. Hay que utilizar diuréticos tiazídicos en dosis de 25-50 mg/día si el clearance de creatinina es mayor de 50 ml/minuto o reemplazarlos por diuréticos de asa (si es menor a 30 ml/min). La furosemida se administra en dosis de 20-80 mg/día, repartida en 2-3 tomas diarias[53] pues la intensa natriuresis que dura 6-8 horas que provoca la administración de una sola dosis diaria puede ser seguida por la retención reactiva de sodio mediada por el sistema renina-angiotensina-aldosterona con el consecuente inadecuado control de la PA. La torsemida, diurético de asa de acción prolongada puede administrarse en dosis de 2,5-5 mg en una sola toma diaria, pero tiene un mayor costo. Si el paciente continúa con cifras tensionales elevadas se deberá reevaluar el esquema terapéutico administrando combinaciones de drogas de distintas familias de fármacos teniendo en cuenta los posibles mecanismos fisiopatológicos que pueden participar. Así, se reducirá la sobrecarga de volumen aumentando la dosis de diuréticos tiazídicos o de furosemida, y agregando antagonistas de la aldosterona, disminuyendo la sobreactividad simpática mediante β-bloqueantes), y alfa y beta-bloqueantes, reduciendo la resistencia vascular (IECA, BRA) o por medio de la relajación del músculo liso vascular (antagonistas del calcio, o vasodilatadores directos)[54]. La importancia de agregar agentes anti-aldosterona en los pacientes con hipertensión resistente se vio reforzada con la comprobación que la hormona pro-

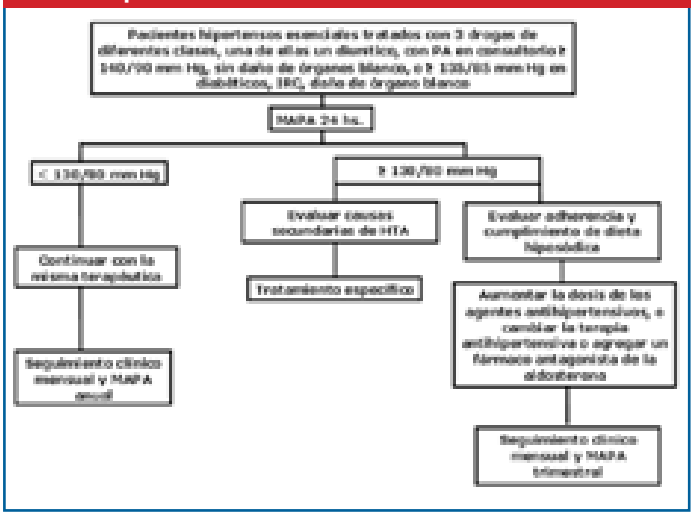
duce hipertensión no solo por la retención de sodio con la consecuente hipervolemia, sino por sus efectos vasoconstrictores directos y por alteración de la complacencia vascular[55]. Ouzan y col[56] trataron con espironolactona a 25 pacientes con hipertensión resistente y observaron un descenso significativo de la PA sistólica y diastólica por medio del MAPA al mes de tratamiento, y una marcada disminución del número de fármacos utilizados para controlar la PA a los 3 meses de tratamiento, sin efectos renales adversos. Nishizaka y col[57] confirmaron esos resultados en un estudio prospectivo agregando dosis bajas de espironolactona (12,5-50 mg diarios) a la medicación antihipertensiva administrada, en pacientes que cumplían los criterios de hipertensión resistente, con o sin diagnóstico de hiperaldosteronismo primario. Después de un seguimiento de 6 meses la espironolactona redujo la PAS en 25±20 mm Hg y la PAD en 12±12 mm Hg, sin comprobar diferencias entre los pacientes con aldosteronismo primario y aquellos sin esa enfermedad. Estos autores comprobaron una fuerte asociación entre el exceso de aldosterona y el deterioro de la función endotelial. En consecuencia, se postuló que el bloqueo de la aldosterona puede actuar en parte por reversión por lo menos parcial de la disfunción endotelial y aumento de la formación de óxido nítrico. La espironolactona se halla contraindicada en pacientes con falla significativa de la función renal o hiperkalemia. Se debe recordar que la administración de esa droga con IECAs o AINEs se asocia con severa hiperkalemia. Una alternativa a la espironolactona es la eplerenona, un bloqueante del acoplamiento de la aldosterona al receptor mineralocorticoide, que se administra a la dosis inicial de 50 mg una vez al día. Esa dosis deberá reducirse a 25 mg/día en el caso que el paciente se encuentre recibiendo medicamentos que comparten la misma vía metabólica de la CYP3A4 (konazoles, eritromicina, verapamil, saquinavir). Weinberger y cols[58] en hipertensos hiporreninémicos, y White y cols[59] en ancianos con HTA sistólica hallaron que la eplerenona tuvo mayor eficacia que losartan y similar efectividad que la amlodipina en esos pacientes con HTA de difícil manejo o con hipertensión resistente. Su administración está contraindicada si el clearance de creatinina es<30 ml/min. Otros agentes antihipertensivos que pueden ser de utilidad para el tratamiento de las hipertensión resistente son los vasodilatadores directos, como la hidralazina y el minoxidil. Esas drogas deben ser consideradas como tratamientos de cuarta o quinta línea y, en el caso de utilizarse se deberá ajustar la dosis del diurético para prevenir la retención hidrosalina[60].

Si a pesar de todas esas medidas no se logra un adecuado control y hay evidencias de daño de órganos nobles, puede considerarse la selección del tratamiento basado en estudios hemodinámicos no invasivos como la bioimpedancia torácica[61].

Se halla aún en etapa de investigación el beneficio de enfoques no farmacológicos como el equipo Rheos (CVRx, Maple Grove, MINN, USA) que estimula a los barorreceptores carotídeos para lograr un mejor control de la PA[62].

Una cuidadosa evaluación de la adherencia a la medicación constituye un paso fundamental en el enfoque de la hipertensión resistente, Puede mejorarse sustancialmente por medio de un seguimiento telefónico o por medio de emails en el que se encuentren involucrados enfermeras y otros miembros del equipo de salud, y que permita recordar a los pacientes la necesidad de efectuar adecuadamente la medicación y conocer mas asiduamente si se presentan potenciales efectos adversos.

Figura 1. Algoritmo para el diagnóstico y manejo de la hipertensión resistente



Referencias

1. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure: the JNC VII report. JAMA 2003; 289: 2560-72. (Erratum, JAMA 2003; 290: 197).
2. Cifkova R, Erdine S, Fagard R. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. J Hypertens 2003; 21: 1779-1786.
3. Hyman DJ, Pavlik VN. Characteristic of patients with uncontrolled Hypertension in the United States. N Engl J Med. 2001; 345: 479-86.
4. Andersson O, Berglund G, Hansson L, et al. Organization and efficiency of an out-patient hypertension clinic. Acta Med Scand. 1978; 203: 391-398.
5. Beilin LJ, Bulpitt CJ, Coles EC, et al. Long-term antihypertensive drug treatment and blood pressure control in three hospital hypertension clinics. Br Heart J 1980; 43: 74-79.
6. Werlemann BC, Offers E, Kolloch R. Compliance problems in therapy resistant hypertension. Herz 2004; 29: 271-275.
7. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart

Attack Trial (ALLHAT). JAMA 2002; 288: 1981-97. [Errata, JAMA 2003; 289: 178, 2004; 291: 2196].

8. Davis BR, Cutler JA, Gordon DJ, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. Am J Hypertens. 1996; 9:342-60.

9. Epstein M. Resistant Hypertension: Prevalence and Evolving Concepts. J Clin Hypertens. 2007; 9: 2-6.

10. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA 2003; 289: 2073-82.

11. Mancia G, Grassi G, Pomidossi G. Effects of blood pressure measurement by the doctor on patients blood pressure and heart rate. Lancet. 1983; 2: 695-698.

12. Pickering TG, James GD, Boddie C et al. How common is white coat hypertension. JAMA. 1988; 259:225.

13. Garg JP, Elliott WJ, Folker A, et al. Resistant hypertension revisited. A Comparison of two University-Based Cohorts . Am J Hypertens. 2005; 18: 619–626.

14. Muxfeldt ES, Bloch KV, da Rocha Nogueira A, Salles GF True resistant hypertension: it is possible to be recognized in the office? Am J Hypertens 2005; 18: 1534-1540.

15. Hermida RC, Ayala D, Calvo C, Lopez JE, Mojon A, Fontao MJ, Soler R, Fernandez JR: Effects of time of day of treatment on ambulatory blod pressure pattern of patients with resistant hypertension. Hypertension 2005; 46: 1053-9.

16. Messerli FH., Ventura HO., Amodeo C. Osler's maneuver and pseudohypertension. N Engl J Med. 1985; 312: 1548.

17. Saltzberg S, Stroh J, Frishman W. Isolated systolic hypertension in the elderly: pathophysiology and treatment. Med Clin North Am. 1988; 72: 523–47.

18. Wright JC, Looney SW. Prevalence of positive Osler's manoeuver in 3387 persons screened for the Systolic Hypertension in the Elderly Program (SHEP). J Hum Hypertens. 1997; 11: 285–89.

19. Kaplan NM. Clinical Hypertension. 9th Ed.Lippincott Williams & Wilkins.2006. pp. 280.

20. Yakovlevitch M, Black HR. Resistant hypertension in a tertiary care clinic. Arch Int Med. 1991; 151:1786–1792.

21. Amar J, Chamontin B, Genes N, et al. Why is hypertension so frequently uncontrolled in secondary prevention? J Hypertens. 2003; 21: 1199-1205.

22. Berlowitz DR, Ash AS, Hickey EC, et al. Inadequate management of blood pressure in a hypertensive population. New Engl J Med. 1998; 339: 1957-1963.

23. Sowers IR, White WB, Pitt B et al. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis and type 2 diabetes mellitus. Arch Intern Med. 2005; 165: 161-8.

24. Zanchetti A, Hansson L, Leonetti G, et al. Low-dose aspirin does not interfere with the blood pressure-lowering effects of antihypertensive therapy. J Hypertens. 2002; 20: 1015-1022.

25. Davies SJC, Ghahramani P, Jackson PR. Panic disorder, anxiety and depression in resistant hypertension – a case-control study. J Hypertension. 1997; 15: 1077-1082.

26. Kaplan NM. Anxiety-induced hyperventilation. A common cause of symptoms in patients with hypertension. Arch Intern Med. 1997; 157: 945-948.

27. Davies SJ, Jackson PR, Ramsay LE, et al. Drug intolerance due to nonspecific adverse effects related to psychiatric morbidity in hypertensive patients. Arch Intern Med. 2003; 163: 592-600.

28. Singer GM, Izhar M, Black HR. Goal-oriented hypertension management: translating clinical trials to practice. Hypertension 2002; 40: 464-469.

29. Shea S, Misra D, Ehrlich MH, et al. Predisposing factors for severe uncontrolled hypertension in an inner-city minority population. N Engl J Med. 1992; 327: 776-781.

30. MacMahon S. Alcohol consumption and hypertension. Hypertension. 1987; 9: 111-121.

31. Stammler R., Caggiula A., Grandist G. Relation of body mass and alcohol, nutrient, fiber and caffeine intakes to blood pressure in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. Am J Clin Nutr. 1997; 65: 338S - 365S.

32. Gordon T, Kannel WB. Drinking and its relation to smoking, blood pressure, blood lipids and uric acid. Arch Intern Med. 1983; 143: 1366-1374.

33. Rakic V, Puddey IB, Burke V, et al. Influence of pattern of alcohol intake on blood pressure in regular drinkers: A controlled trial. J Hypertens. 1998; 16: 165-174.

34. Henningsen NC, Ohlsson O, Mattiasson I, et al. Hypertension, levels of gamma-glutamyltranspeptidase and degree of blood pressure control in middle-aged males. Acta Med Scand. 1980; 207: 245-251.

35. Greenberg G., Thompson S., Brennan P. The relationship between smoking and the response to antihypertensive treatment in mild hypertension in the Medical Research Council's Trial of Treatment. Intern J Epidemiol. 1987; 16: 25-30.

36. Bramlage P, Pittrow D, Wittchen HU, et al. Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. Am J Hypertens. 2004; 17: 904-10.

37. van Jaarsveld BC, Krijnen P, Derkx FH, et al. Resistance to antihypertensive medication as predictor of renal artery stenosis: comparison of two drug regimens. J Hum Hypertens. 2001; 15: 669-676.

38. Wofford MR, King DS, Wyatt SB, et al. Secondary hypertension: detection and management for the primary care provider. J Clin Hypertens. (Greenwich). 2000; 2: 124-31.

39. Anderson GH Jr., Blakeman N, Streeten DH. The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. J Hypertens. 1994; 12: 609-15.

40. Logan AG, Perlikowski SM, Mente A. High prevalence of unrecognized sleep apnea in drug-resistant hypertension. J Hypertens. 2001; 19: 2271-2277.

41. Lavie P, Hoffstein V. Sleep apnea syndrome: a possible contributing factor to resistant hypertension. Sleep. 2001; 24: 721-725.

42. Wolk R, Shamsuzzaman AS, Somers VK. Obesity, sleep apnea and hypertension. Hypertension. 2003; 42: 1067-1074.

43. Dimsdale JE, Coy T, Ziegler MG, et al. The effect of sep apnea on plasma and urinary catecholamines. Sleep. 1995; 18: 377-381.

44. Phillips BG, Narkiewicz K, Pesek CA, et al. Effects of obstructive sleep apnea on endotelin-1 and blood pressure. J Hypertens. 1999; 17: 61-66.

45. Winnicki M, Shamsuzzaman A, Lanfranchi P, et al. Erythropoietin and obstructive sleep apnea. Am J Hypertens. 2004; 17: 783-786.

46. Calhoun DA, Nishizaka MK, Zaman MA. Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea. Chest. 2004; 125: 112-117.

47. Goodfriend TL, Calhoun DA. Resistant hypertension, obesity, sleep apnea, and aldosterone. Hypertension. 2004; 43: 518-524.

48. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39: S1-S266.

49. Stevens L, Coresh J, Greene T, et al. Assessing kidney function-measured and estimated glomerular filtration rate. N Engl J Med. 2006; 354: 2473-83.

50. Brown MA, Buddle ML, Martin A. Is resistant hypertension really resistant? Am J Hypertens. 2001; 14: 1263-69.

51. Graves JW, Bloomfield RI, Buckalew VM Jr. Plasma volume in resistant hypertension: guide to pathophysiology and therapy. Am J Med Sci. 1989; 298: 361-5.

52. Graves JW, Bloomfield RI, Buckalew VM Jr. Plasma volume in resistant hypertension: guide to pathophysiology and therapy. Am J Med Sci. 1989; 298: 361-5.

53. Finnerty FA, Maxwell MH, Lunn J, et al. Long-term effects of furosemide an hydrochlorothiazide in patients with essential hypertension: a two-year comparison of efficacy and safety. Angiology. 1977; 28: 125-33.

54. Moser M, Setaro JF. Resistant or difficult to control hypertension. N Engl J Med. 2006; 355: 385-392.

55. Lacolley P, Labat C, Pujol A. Increased carotid wall elastic modulus and fibronectin in aldosterone-salt-treated rats. Circulation. 2002; 106: 2848-2853.

56. Ouzan J, Perault C, Lincoff M, et al. The role of spironolactone in the treatment of patients with refractory hypertension. Am J Hypertens. 2002; 15 N: 333-339.

57. Nishizaka M, Zaman MA, Calhoun D. Efficacy of low dose spironolactone in subjects with resistant hypertension. Am J Hypertens. 2003; 16: 925-930.

58. Weinberger MH, White WB, Ruilope LM. Effects of eplerenone versus losartan in patients with low renin hypertension. Am Heart J. 2005; 150: 426-433.

59. White WB, Duprez D, Hillaire R. Effects of the selective aldosterona blocker eplerenone versus the calcium antagonist amlodipine in systolic hypertension. Hypertension. 2003; 41: 1021-1026.

60. Sica DA. Minoxidil: an underused vasodilator for resistant or severe hypertension. J Clin Hypertens (Greenwich). 2004; 6: 283-287.

61. Taler SI, Textor SC, Augustine JE. Resistant hypertension. Comparing hemodynamic management to specialist care. Hypertension. 2002; 39: 982-988.

62. Lohmeier TE, Dwyer TM, Hildebrandt DA, et al. Influence of prolonged baroreflex activation on arterial pressure in angiotensin hypertension. Hypertension. 2005; 46: 1194-1200.

Management of metabolic syndrome in young population

Ayrton Pires Brandão, MD, Associate Professor of Cardiology, State University of Rio de Janeiro
Andréa Araújo Brandão, MD, Associate Professor of Cardiology, State University of Rio de Janeiro
Maria Eliane Campos de Magalhães, MD, Associate Professor of Cardiology, State University of Rio de Janeiro
Roberto Pozzan, MD, Associate Professor of Cardiology, State University of Rio de Janeiro

Corresponding author:
Ayrton Pires Brandão, MD, FACC, Associate Professor of Cardiology, State University of Rio de Janeiro. Address: Rua Abade Ramos 107 ap. 101. Jardim Botânico - Rio de Janeiro (RJ). CEP 22461-090. Brazil. Tel: 5521-22861467 Fax: 5521-25372729 E-mail; brandao.trp@terra.com.br

Recibido: 12/02/2007 Aceptado: 13/04/2007

Abstract

Metabolic Syndrome is a complex disorder associated with several cardiovascular risk factors resulting in a 2.5-fold increase in cardiovascular mortality in adults. However, over the last 20 years, the same association has been demonstrated in the young population and it is also related to a parental history of the syndrome. However, the root of the problem could be a high risk factor profile for metabolic syndrome in children and adolescents as it has been demonstrated over the last 20 years. It has been shown that the association of obesity, alterations on glucose and lipids metabolism and high blood pressure are responsible for early atherosclerotic lesion at autopsy observed in young people. The prevalence of several risk factors for cardiovascular diseases has increased in the Brazilian population, as has that of obesity, a cause of great concern due to its importance as one of the metabolic syndrome components. The anthropometrics patterns of the Brazilian population have changed over the last 30 years from undernourishment to weight excess, regardless of age, sex and socioeconomic level. The identification of such individuals, followed by primary preventive measures, changes in lifestyle, and the pharmacological treatment should be implemented aiming at reducing the cardiovascular risk in countries undergoing an economic transition, such as Brazil. The measures recommended for that age group should be focused on changing the life style trough out adoption of healthy habits such as avoiding the excessive intake of calories, salt, saturated fat and cholesterol, engagement in regular physical activity without smoking.

Key Words: Metabolic syndrome in young people; Cardiovascular risk; Overweight; Prevention; Cardiovascular disease.

Cardiovascular diseases and metabolic syndrome in underdeveloped countries

Cardiovascular diseases represent the first cause of death in developed countries, but their importance in underdeveloped ones and in those with a transitional economy has increased[1] As responsible, a set of risk factors, identified as metabolic syndrome (MS), represented by arterial hypertension, overweight/obesity, elevated levels of triglycerides, reduced levels of HDL-cholesterol, and intolerance to glucose/type 2 diabetes are rapidly evolving[2,4]. The way such association leads to coronary arteriosclerosis, which accounts for the great majority of the deaths in affected individuals, has not yet been clearly understood. However, one of the important factors is the presence of insulin resistance/hiperinsulinemia, is frequently identified in a cluster in affected individuals. The latter seems to play an important role in the pathophysiology through the activation of the sympathetic nervous system and sodium retention, in addition to stimulation of cell growth. Obesity/hiperinsulinemia seem to be the driving forces related to multiple risk factors and the development of cardiovascular diseases[3,4].

The root of the problem is a high risk factor profile and metabolic syndrome in children and adolescents

The presence of cardiovascular risk factors in the adult population is a common fact in clinical practice. However, over the last 20 years, this same association has been demonstrated in the young population and is also related to a parental history of the syndrome[5,8]. In children and adolescents, the initial alterations in each of such factors may occur in varied associations, which, even being small, ultimately determine an unfavorable cardiovascular profile for those young individuals. Bogalusa carried out a study with 4,522 individuals, whose ages ranged from 5 to 38 years, selected between 1988 and 1996, to assess

the components of the metabolic syndrome (fat index; serum insulin, glucose, triglyceride and HDL-C levels; and BP). The author suggested two independent models to explain the cause of the syndrome. One of the models included fat index and insulin, lipid, and glucose levels, and the other included only insulin levels and blood pressure. The two models explained 54.6% of the total variance in the sample, suggesting a link between the metabolic alteration and the homodynamic factor, whose common substrate was hyperinsulinemia / insulin resistance[8]. Those same clinical alterations could cause the early atherosclerotic lesions at autopsy observed in those population[9-11] .

In Brazil, the Study of Rio de Janeiro, initiated in 1983, was designed to determine the blood pressure curve in 7,015 young individuals aged from 6 to 15 years, stratified by sex and socioeconomic level, and evolved to the search of the aggregation of other cardiovascular risk factors, not only in that population, but also in their relatives. The major results of that study showed a very direct relation between blood pressure and body weight[12], aggregation of blood pressure and body mass between the members of a same family[13], anthropometrics indices, blood pressure and left ventricular mass in adolescents[14], aggregation of blood pressure and metabolic risk factors in adolescents and their relatives[15] and hyperglycemia, hyperinsulinemia, overweight, and elevated blood pressure in young adults[16].

However, of all risk factors of the metabolic syndrome, the presence of overweight/obesity emerges as the most important, especially in the United States, where its prevalence increased 2 to 4 times, particularly among the African Americans and Latin Americans[17]. But this same phenomenon has also been observed in countries with a transitional economy, such as Brazil, as shown in the research carried out by the Brazilian Institute of Geography and Statistics [18], which has confirmed an effective evolution in the anthropometrics-nutritional profile of the entire Brazilian population, including children and adolescents, in the time period between 1974-1975 and 2002-2003 (Figures 1 and 2). In such period, a significant decrease was observed in the prevalence of under nutrition, more marked in the male sex, while a continuous and intense increase was observed in overweight and obesity in both sexes, although greater among women. The findings in children and adolescents should be emphasized: in the same regions and in the same period, the prevalence of undernourished children and adolescents decreased by approximately 50%, while that of overweight/obesity doubled[19,20].

The dietary pattern has also been assessed in that same study, showing that, regardless of their socioeconomic level, Brazilians have a wrong dietary pattern as follows: an excessive amount of sugar, an insufficient amount of fruits and vegetables, and an excessive amount of fat in general, and specially of saturated fat, particularly among the higher-income families living in the most developed regions of the country (South, Southeast, and West Central)[18].

In addition, there is a great tendency towards a sedentary lifestyle, observed in all studies assessing metabolic syndrome, which propitiates the appearance of alterations related to the glucose and lipid metabolism and an increase in blood pressure, which are well-known important risk factors for the development of cardiovascular diseases. Such findings point to a real probability of an increase in the future cardiovascular morbidity and mortality rates, which have a great socioeconomic impact not only for Brazil, but also for all countries with a transitional economy.

Table 1. Components of metabolic syndrome according to NCEP-ATP III

Components	Defining level
Abdominal obesity, given as waist circumference	
Men	>102cm
Women	>88cm
Triglycerides	≥150mg/dL
HDL Colesterol	
Men	<40mg/dL
Women	<50mg/dL
Blood pressure	≥130mmHg / ≥85mmHg
Fasting glucose	≥110mg/dL

Table 2. Goals for the treatment of metabolic syndrome in young people

Glucose (mg/dL)	
Fasting glucose	<100mg/dL
Impaired glucose tolerance (2h)	<140mg/dL
HgA1c (%) in diabetes	<7%
Cholesterol (mg/dL)	
Total	<170mg/dL
HDL-c	>40mg/dL
LDL-c	<110mg/dL
Triglycerídes (mg/dL)	<150mg/dL
Blood Pressure (mmHg)	
Systolic	<130mmHg
Diastolic	<80mmHg
Weight (kg)	Weight reduction 5-10%

Therapeutic approach

Although MS comprises variables that increase the risk for cardiovascular diseases, there is a lack of specific prospective studies about that syndrome that allow the elaboration of a table of risk similar to that of the Framingham study. However, because of its high unfavorable prognostic potential, MS should be

treated seriously, as earlier as possible, as should the other risk factors occasionally present, aiming at reducing the significant cardiovascular risk associated with that condition.

The goals for the treatment of MS are shown in table 2[21]. It is worth emphasizing that its success will depend on the patient's commitment, the persistence of the health professional, and the socioeconomic conditions of those involved. This objective requires non-pharmacological and pharmacological therapeutic measures.

Non-pharmacological treatment

Non-medicaments measures aiming at a change in lifestyle, focusing on regular physical activity and a balanced diet, are the first action to be taken[22].

Excessive weight, sedentary lifestyle, and an inappropriate diet are determinants of MS, the correction of such matters being an absolute priority[21].

A well-balanced diet is one of the major measures recommended for individuals with MS, and it should be individualized for the needs of each patient. The diet should be directed to weight loss and a reduction in visceral fat, aiming at normalizing blood pressure levels, correcting dyslipidemia and hyperglycemia, and, consequently, reducing the cardiovascular risk. Evidence favors fiber-rich diets with a low content of saturated fat and cholesterol, and a reduced amount of simple sugars[21,23]. The Mediterranean diet[24] proved to reduce cardiovascular events, and the DASH diet[25] proved to reduce blood pressure levels.

At first, a diet abiding by all those recommendations is of difficult acceptance, leading to low patient's compliance. Therefore, the dietary guidance should, whenever possible, consider the socioeconomic and cultural habits of each individual. The help of a nutritionist may be useful to improve the dietary planning and to increase the patient's adherence to treatment. The total caloric value should be calculated so that the pre-established weight may be reached, considering that even a 5% to 10% reduction in weight is associated with an improvement in blood pressure levels, in metabolic control, and even in the diabetes-related mortality.

Physical activity should also be strongly stimulated, always considering each individual's age group and fitness[26]. The practice of moderate exercise for 30-40 minutes per day is undoubtedly associated with cardiovascular benefit. More intense physical activities are usually required to induce greater weight loss, and, in such cases, both for the type and intensity of the exercise, patients should be individually assessed and occasionally undergo cardiovascular evaluation.

Excessive ingestion of alcoholic beverages is related to an increase in blood pressure and triglyceride levels, and in the total caloric load[27]. A limit of alcohol ingestion of 30 mL/day is recommended for men and 15 mL/day for women.

Pharmacological treatment

The medicaments treatment may be necessary and, although it should not desirable, it has been increasingly used in young patients with elevated blood pressure, dyslipidemia, and diabetes[28]. The use of medication to treat obesity may also be considered, although the experience is still small and lacks a long-term assessment[28].

The pharmacological treatment is always indicated when no satisfactory therapeutic response is obtained with the non-pharmacological measures.

Hypertension

Decrease in blood pressure levels reduces the cardiovascular and renal morbidity and mortality. Therefore, any of the following 5 major classes of antihypertensive drugs should be used for the initial treatment of arterial hypertension: diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers[29]. Those drugs do not significantly differ regarding the cardiovascular benefits. Depending of the blood pressure level most studies assessing blood pressure control have reported that the majority of patients were on an association of anti-hypertensive drugs.

Blockade of the renin-angiotensin system has proved to be useful for the MS treatment when diabetes is present[30]. Some clinical studies on diabetic nephropathy with proteinuria have shown that renal protection is beneficial in type-1 (ACEI) and type-2 (angiotensin-receptor blocker) diabetic individuals[31].

In hypertensive individuals with BP ≥160/100mmHg, the combination of drugs should be considered since the beginning of the antihypertensive treatment. In approximately two thirds of the hypertensive patients, 2 or more drugs are required for blood pressure control, especially when the blood pressure levels are more elevated or when the goals to be achieved are strict. When drugs are combined, a diuretic should be used.

In patients with MS, a blood pressure reduction to levels lower than 130/85mmHg may be useful, considering the elevated cardiovascular risk associated with hypertension. In a type-2 diabetic patient, blood pressure should be reduced to a level below 130/80mmHg, regardless of the drug combination necessary for achieving that objective. The presence of nephropathy with important proteinuria is indicative for a reduction in blood pressure to values below 120/75mmHg[31].

Type 2 diabetes

Most patients with hyperglycemia do not properly respond to the non-pharmacological treatment. In

such cases, one or more hypoglycemic agents should be introduced to control glycemia and promote a decrease in the glycosylated hemoglobin A1c level[32] .

Diabetes is currently considered a cardiovascular disease. This change in paradigm implies a new direction in the treatment of the disease. In addition to the objective of normalizing glycemia, strategies should be directed to reducing the incidence of cardiovascular events. The adoption of stricter goals, not only in regard to glycemic levels, but also to the other associated risk factors, should be sought[33]. In regard to the oral hypoglycemic agents used in the treatment of type 2 diabetes, the ideal drug should have, in addition to the antihyperglycemic effect, an antiatherogenic action.

Type 2 diabetes results from the following 2 basic defects: insulin resistance and insulin deficiency. In the initial phases of the disease, the factor "insulin resistance" predominates, and the use of insulin-sensitizing drugs, such as metformin and glitazones, is indicated. Acarbose can also be used in that situation.

The natural history of type 2 diabetes shows that, as years go by, a progressive deterioration in glycemia occurs due to the installation of insulin deficiency. In this phase, sulfonylureas may be used in association with insulin sensitizes. Insulin deficiency may worsen, requiring the association of insulin with oral agents, and, finally, therapy with insulin alone.

Glinides and acarbose are auxiliary drugs indicated for the treatment of postprandial hyperglycemia.

Therapeutic combinations of metformin and glitazones, metformin and sulfonylureas, and glitazones and sulfonylureas have been widely used.

Dyslipidemias

The alterations in the lipid metabolism frequently bear a relation to atherogenesis, and, consequently, to atherosclerosis, and to high cardiovascular morbidity and mortality rates[27,34].

The goals of the treatment of a patient with MS regarding lipid levels are shown in table 2. It is worth emphasizing that although LDL-cholesterol levels are not one of the diagnosing criteria of MS, controlled clinical trials have reported the need for reducing LDL-cholesterol as a primary goal to be achieved with treatment, simultaneously with the correction of the HDL-cholesterol and triglyceride levels[28].

Statins are the drugs of choice to reduce LDL-cholesterol. Studies on primary and secondary prevention in adults have shown that statins reduce coronary events, the incidence of stroke, the need for myocardial revascularization, and total cardiovascular mortality[28]. Fibrates have proved to be beneficial in reducing cardiovascular events in individuals with HDL-cholesterol below 40 mg/dL, a frequent component of MS. Fibrates have also been indicated for the treatment of hypertriglyceridemia when diet and physical activity were not sufficient to correct it. Ezetimibe in association with statins causes a marked reduction in LDL-cholesterol and may be used to achieve the recommended lipid goals. The combined therapy of statins and fibrates or nicotinic acid may be an attractive option for individuals with MS who have elevated LDL-cholesterol and triglyceride levels and reduced HDL-cholesterol levels. Care should be taken regard the continuous use of statins and fibrates and Creatinophosfokinase levels should be measured 1, 3, and 6 months. If patients are stable, measurements can be repeated every 6 months. In the presence of myalgia this combination should be discontinued.

Obesity

If the non-pharmacologic measures recommended do not reduce weight by at least 1% of its initial value per month, after 1 to 3 months, the introduction of adjuvant drugs should be considered for individuals with a BMI ≥30kg/m^2, or for those with a BMI between 25kg/m^2 and 30kg/m^2 in the presence of co morbidities. Sibutramine and orlistat are the most frequently indicated drugs. Some studies have reported their favorable effects on weight loss and improvement in metabolic parameters with good tolerance and safety[35]. Drugs of the noradrenergic class, the selective serotonin reuptake inhibitors used as antidepressants are effective for weight loss but studies testing them are old and relating to the short time.

The importance of primary prevention in children and adolescents

The adoption of primary preventive measures in young individuals has been recognized as of great importance in approaching cardiovascular diseases. The demonstration of the presence of arteriosclerosis in children, adolescents, and young adults, in addition to a greater knowledge about the risk factors in those age groups, points to proposals of rational and effective programs aiming at interfering with those factors as early as possible[35,37].

The measures recommended for that age group focus on the adoption of healthy habits, such as avoiding the excessive ingestion of calories, salt, saturated fat, and cholesterol, and engaging in regular physical activity without smoking and control on alcohol intake. Health education focusing on improving nutrition, physical activity and healthy lifestyles for school children and their parents should become a leading role for physicians[38,39].

The specific prevention of obesity through diet and physical activity should be the number one priority, because its success will have a positive direct repercussion on dyslipidemia, arterial hypertension, and the alterations in the metabolism of carbohydrates[22,38,39].

The benefits associated with physical activity in young individuals include weight loss, improvement in met-

abolic parameters, a reduction in blood pressure and insulin resistance, psychic wellbeing, predisposition to maintain physical activity in adulthood, and, consequently, a decrease in the risk of cardiovascular disease and an increase in life expectancy[22,39].

In general, youngest people have been exercising less. Television, videogames, and computers tend to keep them indoors. The lack of safety in big cities inhibits walking and bike riding. At school, the new curricular requirements have reduced the time spent for physical activity. And, finally, the families have become increasingly sedentary. These observations point towards the need for actions directed to changes in the family as a whole.

Governmental programs providing specific areas for practicing physical exercise, a greater supply of physical education teachers, and improved public safety are absolutely necessary. It is also a consensus that such measures will only succeed within a context encompassing joint family, school, community, and government efforts.

Only interference at young age will be able to effectively guarantee a healthy adult lifestyle, as far as the cardiovascular system is concerned, thereby favorably influencing the elevated cardiovascular morbidity and mortality rates.

References

1. Lakka HM, Laaksonen DE, Lakka TA, et al: The metabolic syndrome and total cardiovascular disease mortality in middle-aged men. JAMA. 2002;288:2709-716.
2. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. Circulation. 2002;106:3143-421.
3. Grundy SM, Brewer B, Cleeman JI, et al: Definition of the metabolic syndrome. Report of the National Heart, Lung and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. Circulation. 2004;109:433-38.
4. Brandão AP, Nogueira AR, Oliveira JE, et al: I Diretriz Brasileira de Diagnóstico e Tratamento da Síndrome Metabólica. Arq Bras Cardiol. 2005;84(supl I):1-28.
5. Berenson GS, Srinivasan SR, Bao W, et al: Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Eng J Med. 1998;338:23:1650-656.
6. Srinivasan SR, Myers L, Berenson GS: Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (Syndrome X) in young adulthood: The Bogalusa Heart Study. Diabetes. 2002;51:204-209.
7. Steinberger J, Daniels SR: Obesity, insulin resistance, diabetes and cardiovascular risk in children. Circulation. 2003;107:1448-453.
8. Chen W, Srinivasan SR, Elkasabany A, et al: The association of cardiovascular risk factor clustering related to insulin resistance syndrome (Syndrome X) between young parents and their offspring: The Bogalusa Heart Study. Atherosclerosis. 1999;145:197-205.
9. Berenson GS, Wattigney W, Tracy R, et al: Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (the Bogalusa Heart Study). Am J Cardiol. 1992;70:851-58.
10. Xiangrong L, Shengxu L, Ulosoy E, et al: Childhood adiposity as a predictor of cardiac mass in adulthood. The Bogalusa Heart Study. Circulation. 2004;110:3488-492.
11. MacMahan CA, Gilding SS, Fayad ZA, et al: Risk score predict atherosclerotic lesions in young people. The Pathological Determinants of Atherosclerosis in Youth Research Group. Arch Intern Med. 2005;165:883-90.
12. Brandão AP, Brandão AA, Araujo EMM, et al: The significance of physical development on blood pressure curve of children between 6 and 9 years of age and its relationship with familial aggregation. J Hypertens. 1989;7(suppl 1):S37-S39.
13. Brandão AP, Brandão AA, Araujo EMM, et al: Familial aggregation of arterial blood pressure and possible genetic influence. Hypertension. 1992;9(suppl II):II-214-17.
14. Brandão AA, Pozzan R, Albanesi Fº FM, et al: Role of anthropometric indexes and blood pressure as determinants of left ventricular mass and geometry in adolescents: The Rio de Janeiro Study. Hypertension. 1995;26:1190-194.
15. Magalhães MEC, Pozzan R, Brandão AP, et al: Early blood pressure level as a mark of familial aggregation of metabolic cardiovascular risk factors – The Rio de Janeiro Study. J Hypertens. 1998;16:1885-889.
16. Pozzan R, Brandão AA, Brandão AP, et al: Hyperglycemia, hyperinsulinemia, overweight, and high blood pressure in young adults: The Rio de Janeiro Study. Hypertension. 1997;30(3pt2):650-53.
17. Weiss R, Dziura J, Burgert TS, et al: Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350:2362-374.
18. Instituto Brasileiro de Geografia e Estatística (IBGE). [homepage on the internet]. Análise da disponibilidade domiciliar de alimentos e do estado nutricional no Brasil. [acesso em março de 2005]. Disponível em <http://www.ibge.gov.br>
19. Monteiro CA, Mondini L, Souza ALM, et al: The nutrition transition in Brazil. Eur J Clin Nutr. 1995;49:105-13.
20. Caballero B: Global health: A nutrition paradox underweight and obesity in developing countries. N Engl J Med. 2005;352:1514-516.
21. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Cholesterol. JAMA. 2001;285:2486-497.
22. Ard JD, Grambow SC, Liu D, et al: The effect of the PREMIER interventions on insulin sensitivity. Diabetes Care. 2004;27(2):340-47.
23. Riccardi G, Rivellese AA: Dietary treatment of the metabolic syndrome – the optimal diet. Br J Nutr. 2000;83(suppl 1):S143-S148.
24. De Lorgeril M, Renaud S, Mamelle N, et al: Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet. 1994;343:1454-459.
25. Sacks FM, Svetkey LP, Vollmer WM, et al: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001;344:3-10.
26. Ross R, Freeman JA, Janssen I: Exercise alone is an effective strategy for reducing obesity and related comorbidities. Exerc Sport Sci Rev. 2000;28:165-70.
27. Grundy SM, Hansen B, Smith Jr S, et al: Clinical management of metabolic syndrome. Report of the American Heart Associa-

tion/National Heart, Lung and Blood Institute/American Diabetes Association Conference on Scientific Issues Related to Management. Circulation. 2004;109:551-56.

28. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. Circulation. 2002;106:3143-421.

29. Chobanian AV, Bakris GL, Black HR, et al: National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-252.

30. UK Prospective Diabetes Study Group. Tight blood pressure control and the risk of macrovascular and microvascular complications in type diabetes. (UKPDS 38). BMJ. 1998;317:703-13.

31. Lewis EJ, Hunsicker LG, Clarke WR: Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851-60.

32. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65.

33. Lebovitz HE (ed): Therapy for Diabetes Mellitus and Related Disorders. American Diabetes Association. 4th ed. Alexandria, VA, USA; 2004.

34. Grundy SM, Hansen B, Smith Jr S, et al: Clinical management of metabolic syndrome. Report of the American Heart Association/National Heart, Lung and Blood Institute/American Diabetes Association Conference on Scientific Issues Related to Management. Circulation. 2004;109:551-56.

35. Arterburn DE, Crane PK, Veenstra DL: The efficacy and safety of sibutramine for weight loss: a systematic review. Arch Intern Med. 2004;164:994-1003.

36. US National Institute of Health: Clinical Guidelines on the Identification, Evaluations and Treatment of Overweight and Obesity in Adults: Executive summary. Expert Panel on the Identification, Evaluation and Treatment of Overweight in Adults. Am J Clin Nutr. 1998;68(4):899-917.

37. MacLean LD, Rhode BM, Sampolis J, et al: Results of the surgical treatment of obesity. Am J Surg. 1993;165(1):155-62.

38. Downey AM, Frank GC, Webber LS, et al: Implementation of "Heart Study": A cardiovascular school health promotion program. J Sch Health. 1987;57:98-104.

39. Hayman LL, Wiliams CL, Daniels SR, et al: Cardiovascular health promotion in the schools. Circulation. 2004;110:2266-275.

Molecular mechanisms of Endothelial Dysfunction: from the nitric oxide synthesis to ADMA inhibition

Valmore Bermúdez. MD; PhD1., Fernando Bermúdez. MD; PhD1., Guillermo Acosta. MD1. , Alejandro Acosta. MSc1., Johnny Añez. MSc1, Carla Andara. MSc1., Elliuz Leal. MD1., Clímaco Cano. PharmD1, Velasco Manuel. MD, PhD2, Rafael Hernández. MD, PhD3, Zafar Israili. PhD4

1: Endocrine and Metabolic Diseases Research Center. University of Zulia. School of Medicine. Maracaibo, Venezuela.
2: Clinical Pharmacology Unit, Vargas Medical School, Central University of Venezuela, Caracas, Venezuela.
3: Clinical Pharmacology Unit, School of Medicine, Universidad Centroccidental Lisandro Alvarado, Barquisimeto, Venezuela
4: Emory University School of Medicine. Atlanta, GA. USA.

Short Title: MOLECULAR MECHANISM OF ENDOTHELIAL DYSFUNCTION

Address correspondence: Valmore Bermúdez, MD; PhD. La Universidad del Zulia, Facultad de Medicina, Escuela de Medicina, Centro de Investigaciones Endocrino-Metabólicas "Dr. Félix Gómez".
e-mail: Vbermudez@hotmail.com; fago@medscape.com

Recibido: 20/03/2007 *Aceptado: 25/04/2007*

Abstract

Endothelial dysfunction symbolize several pathological conditions, including altered anticoagulant and anti-inflammatory properties of the endothelium, impaired modulation of vascular growth, and dysregulation of vascular remodeling. Nevertheless, this term has been used commonly to refer to an impairment of endothelium-dependent vasorelaxation caused by a loss of nitric oxide bioactivity.

The clinical and scientific relevance of Nitric Oxide synthesis and bioavailability in endothelial dysfunction is based on the fact that it is a common factor in the pathogenesis of cardiovascular diseases. These alterations have been demonstrated in both animal models and humans, in the scope of dangerous pathological conditions as cigarette smoking, hypertension, hypercholesterolemia, aging, diabetes and heart failure.

A decline in Nitric Oxide bioavailability may be caused by decreased expression of the endothelial NO synthase, a reduction of substrate or cofactors for this enzyme, alterations of cellular signaling, enzyme inhibition by asymmetric dimethyl arginine and, finally, accelerated Nitric Oxide degradation by reactive oxygen species.

The knowledge of the processes related to these alterations becomes of remarkable importance for the understanding and of the generation of innovating and effective therapeutic strategies for cardiovascular diseases.

Key Words: Nitric Oxide, Nitric Oxide Synthase, Endothelial Dysfunction, Cardiovascular Diseases.

Introduction

Vascular endothelial cells constitute a structurally simple, but functionally complex organ which regulates a number of processes as hemostasis, fibrinolysis, inflammation, blood pressure, lipoproteins metabolism and angiogenesis, and in this way, it plays an essential role in the homeostasis of the vascular system. Alterations presented in one or more of these physiological phenomena are what it is known as endothelial dysfunction[1] (Figure 1). Even though, the association between several risk factors and cardiovascular diseases is well documented, it is often observed that some individuals who present some of these factors do not develop cardiovascular diseases, which suggests there is an "activating connector" that once affected significantly joins risk factors with cardiovascular pathologies through some anomalous processes. Due to it's strategically location and its biological properties, vascular endothelial cells constitute this "hot key" in the chain of events that ends in vascular system dysfunction[2]. Endothelium-dependent relaxation alteration by a decrease in both, synthesis and/ nitric oxide (NO) bioavailability constitute the earlier and most important phenomenon in endothelial dysfunction[3]. Nitric oxide carries out important functions related to the vascular system homeostasis such as vessel tone regulation, inhibition of platelet aggregation, leukocyte's adhesion and transmigration inhibition, as well as the proliferation and migration of smooth muscle cells. Hence, the decrease of this molecule's activity constitutes a major element in the pathophysiological processes that ending in cardiovascular atherosclerotic related diseases[4]. However, these transformations, besides being complex and diverse have not been completely clarified[5].

Figura 1

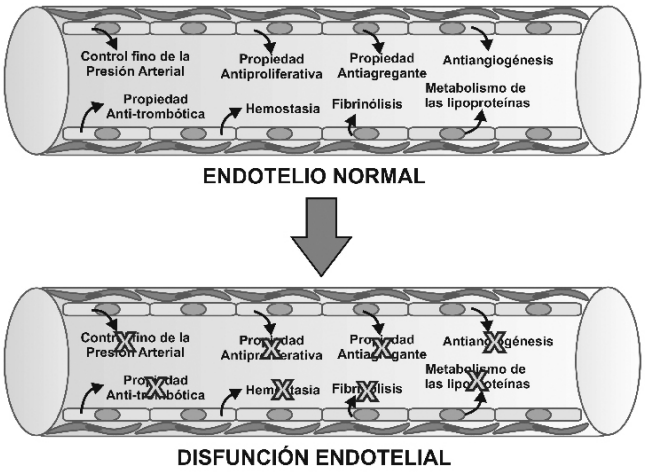


Figura 1: Disfunción Endotelial. El endotelio en condiciones normales emite múltiples señales moleculares que le conceden propiedades antiagregante plaquetaria, antitrombótica y antiaterogénica, lo cual lo hace un órgano esencial en el mantenimiento de la homeostasis del sistema vascular. Bajo condiciones patológicas se producen alteraciones en uno o más de los mecanismos de señalización molecular emitidos por éste, lo cual es conocido como disfunción endotelial.

Endothelial nitric oxide synthase (enos) biology

No is a nitrogen-centered free radical produced exclusively by the nitric oxide synthase action (NOS). Three isoforms of this enzyme have been described which are highly homologue in their primary structure. Inducible nitric oxide synthase (iNOS) is expressed in the phagocytic cells by some pro-inflammatory stimuli like cytokines. The two other isoforms are constitutively expressed in nervous tissue (nNOS) and the endothelial cells (eNOS)[6].eNOS synthesizes NO from L-arginine through a oxidation process that involve five electrons transference by means of the intermediary NG-hidroxi-L-arginine[7,8]. The substrates used by this enzyme are the amino acid L-arginine and molecular oxygen and the cofactors required are flavine adenine mononucleotide, tetrahydrobiopterin (BH4), flavine adenine mononucleotide (FMN) and flavine adenine dinuclotide (FAD) nicotinamide adenine dinucleotide phosphate (NADPH). Besides, the last two isoforms contain binding sites for hem group and calmodulin, being both of them essential for its activity. After calcium-calmodulin complex union to eNOS (between the COOH-terminal reductase domain and the NH2-terminal oxydase domain) the electrons are yielded by the NADPH and then transported to oxigenase domain which contains the hem group, which results in citrulin and NO formation[9] (Figure 2).

Figura 2

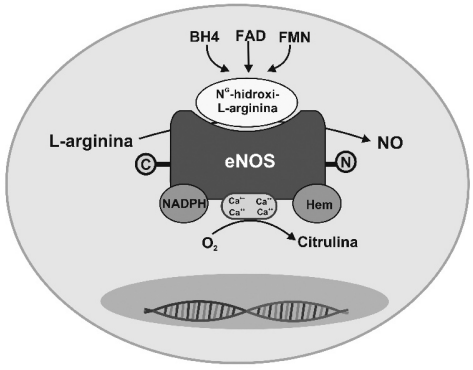


Figura 2: Biología de eNOS. El NO es producido principalmente por los leucocitos, las neuronas y las células endoteliales. En las últimas la eNOS sintetiza NO a partir de su sustrato la L-arginina mediante un paso de oxidación de 5 electrones por medio del intermediario NG-hidroxi-L-arginina.

Molecular mechanisms of endothelial dysfunction

A) Reduction of Nitric Oxide production

- **eNOS transcription Alteration**

Although the term "inducible" has been restricted for iNOS, the expression of eNOS is also regulated by a variety of stimulus[10]. There is extensive evidence about factors which decrease eNOS expression, among which the tumor necrosis factor alpha (TNF-α) is included, which unstabilizes eNOS ARNm, apparently through regulatory proteins affinity increase to the 3' domain of iNOS ARNm molecule[11,12]. Other stimuli that have been reported as ARNm stability reducers include lipopolysaccharide[13], hypoxia[14], and high concentrations of oxidized low density lipoproteins molecules (LDL_{ox})[15] (Figure 3).

Figura 3

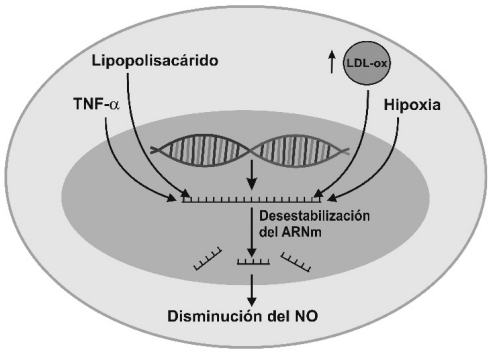


Figura 3: Disminución de la Expresión de eNOS. Diversos elementos propatogénicos como el TNF-α, el lipopolisacárido, la hipoxia y las altas concentraciones del LDL oxidada son capaces de desestabilizar la molécula de ARNm de la eNOS, ocasionando una reducción transcripcional de las concentraciones de eNOS.

- **Alteration in eNOS activity**

Decrease in BH4 intracellular concentrations and Uncoupling phenomena

Under some circumstances eNOS can generate superoxide anion instead NO as a consequence of BH4 concentration decline; this process is known as NADPH oxidation/NO synthesis uncoupling phenomenon[16]. Superoxide radical production is mediated through hem group in eNOS oxygenase domain when arginine and BH4 concentration is relatively low[17,18,19].

Mammals cells can generate BH4 through guanosine triphosphate (GTP) cyclohydrolase I (GTPCH I) enzymatic action[20]. Physiological studies have shown a significant GTPCH I and BH4 activity decrease in various pathological states like insulinresistance, cigarette smoking, and hypercholesterolemia, probably through a LDL_{ox} increase, as well as an expression arise in some pro-inflammatory cytokines (TNF-α and the interleukin-1β)[21,22,23,24] (Figure 4). Furthermore, clinical and experimental studies have confirmed that BH4 acute administration improves endothelial dysfunction related to hypercholesterolemia, atherosclerosis, hypertension and smoking[25-28]. These mechanisms expose an important link between prepathogenic states involved in endothelial dysfunction development.

Figura 4

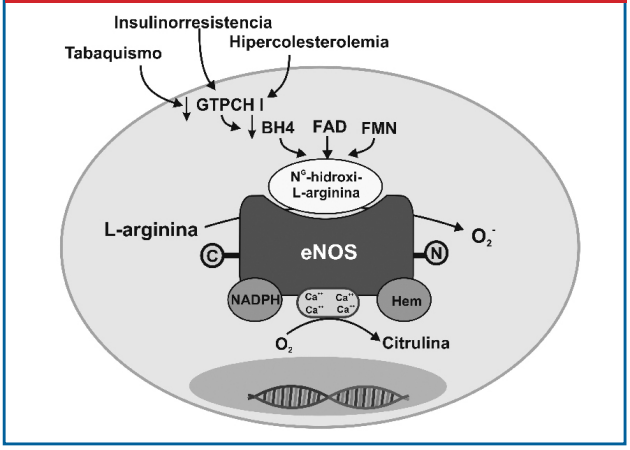


Figura 4: Desacoplamiento de eNOS. Para la síntesis del NO por parte de la eNOS son necesarias concentraciones adecuadas de BH4 y de su sustrato la L-arginina. Cuando alguno de estos factores se encuentra disminuido en cantidad suficiente, la enzima no es capaz de generar NO, produciendo en su lugar un radical libre altamente perjudicial para la biología de las células como es el anión superóxido.

Competitive inhibition of eNOS by asymmetric dimethylarginine

Vallance et al[29] first described in 1992 asymmetric dimethylarginine (ADMA) as a NOS endogenous inhibitor. Since then, the role of this molecule in the regulation of endothelial NO synthesis has increasingly attracted attention. This aminoacid is synthesized in endothelial cells from arginine by an enzyme belonging to arginine protein methyl transferase (PRMTs) family, specifically PRMT-1[30]. Earlier experimental evidence showed that supplementation with L-arginine improves endothelium-dependent vasodilatation impairment in rabbits with hypercholesterolemia and atherosclerosis[31,32], diminishes platelet aggregation[33], inhibits monocyte adhesion[34] and vascular smooth muscle proliferation[35], which is markedly in contrast with both, experimental studies that showed a fail in L-arginine endothelium-dependent vasodilatation stimulation in isolated arterial rings, and in vitro studies showing eNOS saturation at physiological L-arginine concentrations and a failure of exogenous L-arginine administration in achieve an enzyme's activity increment, confirming a lack of L-arginine vasodilator effect in isolated arterial rings[36]. This discrepancy between findings observed in intact animals versus in vitro assays was termed the "L-arginine paradox" that can be explained by the existence of an L-arginine competitive inhibitor now known as ADMA. Thus, administration of L-arginine at high doses should displace ADMA from the eNOS catalytic site and restore NO production to physiological levels in intact experimental models and humans beins[36,37].

The expression and activity of PRMT-1 and in consequence ADMA synthesis is modulated in endothelial cells by a variety of stimuli. For example, an expression increase in this enzyme had been observed in response to LDL[38] molecules and shear stress, conducing to intracellular ADMA concentration. On the other hand, PRMT-1 activity can be blocked by the suppression of a group of protein kinases called kappa beta inhibitors kinase (κβ-IK) that phosphorylates a group of proteins known as kappa beta inhibitors (kβ-I), which once phosphorylated are unable to retain the kβ nuclear factor (kβ-NF) in the cytoplasm, which, then becomes free to translocate to the nucleus, site where exerts its functions as transcription factor[38], suggesting a regulatory interplay by cytokines in the increase of its activity. Besides, multiple pathogenic factors like hypercholesterolemia, hyperglycemia, pro-inflammatory cytokines and hyperhomocysteinemia can diminish the activity of dymethilarginine dymetilaminohydrolase (DDAH), an enzyme responsible of hydrolyzes ADMA degradation, causing a significant intracellular elevation of this aminoacid[38] (Figure 5). Thus, the nexus between cardiovascular disease risk factors, ADMA and endothelial dysfunction are becoming evident in conjunction with the essential role of oxidative stress in atherosclerosis generation.

Figura 5

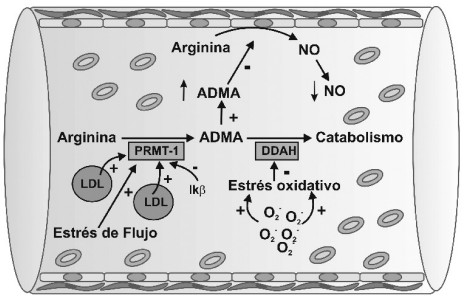


Figura 5: ADMA y Disfunción. La dimetilarginina asimétrica (ADMA) al igual que la L-arginina es un aminoácido que circula en el plasma, es excretado por la orina, y es encontrado en células y tejidos. Cuando las concentraciones de la primera (ADMA) exceden las de la segunda (L-arginina), se produce una inhibición competitiva de la síntesis de NO por parte de eNOS que conduce a la génesis de la disfunción endotelial.

Lipids and Caveolae Metabolism

Studies conducted worldwide have indicated that the eNOS location into the cell determines its enzymatic activity. A place of particular importance in the cell for the function of this enzyme is the caveolae[40]. Caveolae is a structure constituted by specialized invaginations in the plasmatic membrane whose main components are cholesterol, glycoesphingolipids,

and a structural protein called caveolin[41]. At present, all evidence indicates that numerous extracellular stimuli exert its signals transduction through this structure[42]. In this sense, eNOS location in caveolae determines its enzymatic activity inhibition by caveolin-1 linkage[43] that cause a blockade in eNOS interaction with the calmodulin when the intracellular calcium levels are low[44]. Also, high levels of oxidized LDL cause a decrease of cholesterol content of caveolae, resulting in caveolin-1-eNOS complex translocation to the cytoplasm, and in consequence, inhibition of its activity[45]. Likewise, there is evidence that hypercholesterolemic serum and native LDL are capable to up regulate caveolin-1 concentration, increasing heterocomplexes formation between eNOS and this protein, diminishing NO production[45]. Furthermore, it is known that some proatherogenic lipids, such as lysophosphatidylcholine and LDL_{ox}, interfere with signal transduction from receptors that activate eNOS[46,48] (acetylcholine receptors, bradykinin, serotonin, histamine and others) (Figure 6). This process enlightens other mechanism which correlates prepathogenic and/or pathological conditions with the decrease of NO levels, and therefore, endothelial dysfunction.

B) Decrease in NO Bioavailability

- **Increase in Arginase activity**

  Arginase is a key enzyme involved in arginine to ornithine (and urea) conversion. This enzyme has two isoforms, arginase I, which is constitutively expressed in the endothelial cells, and arginase II which can be induced by lipopolysacharides and interferon-γ[39]. Thus, systemic or local infectious processes could generate a significant increase on arginase levels causing an important decrease in arginine and consequently a lack in eNOS substrate bioavailability and consequently a failure in NO synthesis.

- **Oxidative stress**

  Even in presence of an adequate NO generation, some circumstances avoid this molecule to reach its biological targets due to a decrease in its bioavailability, as a consequence of the interaction with some chemical compounds[49]. There is abundant experimental evidence indicating the role of NO oxidative inactivation as mediator of endothelial dysfunction and a prepathogenic vascular phenotype[5]. For example, in hyperlipidemia, excessive LDL synthesis entails a concomitant formation of LDL_{ox}, which results in oxidative stress that causes NO conversion to peroxynitrite (chemical specie without the biological effects of NO) by a reaction that proceeds at 6,7 x 10^9 M^1s^{-1}[,51,52]. This velocity is approximately three times higher than the reaction occurring between superoxide and superoxide dismutase (SOD). So that, in a compartment with NO, superoxide and SOD, the superoxide anion is able to react with any of the two other compounds[5]. The results of different studies support the role of the superoxide as essential element in the decrease of NO bioavailability in oxidative stress conditions. In rabbits with aortic atherosclerosis, a remarkable decrease in endothelium-related relaxation was seen (despite an NO synthesis increase up to three times greater in relation to the NO synthesis level in healthy rabbits), which was corrected by SOD treatment[53]. Likewise, ascorbic acid infusion improves the vascular response to the acetylcholine in smokers, diabetic and patients with high blood pressure[50,53].

- **Hyperglycemic Stress**

  Hyperglycemia increases oxygen-derived free radicals production via arachidonic acid metabolism arises. In human aortic endothelial cells, despite the extended exposition to high glucose concentration increases eNOS expression, a concomitantly superoxide anion elevation (probably from NADH/NADPH oxidase) result in NO inactivation. Besides, an extended hyperglycemic stress causes advanced glycosilation endproducts (AGES) accumulation, which is able to inactivate NO. In fact, the alteration in the capacity of endothelium-depending vessels relaxation in diabetic rats can be partially restablished by aminoguanidine (an AGES) administrationr[54,56]. Thus, it is easy to deduce the importance of this mechanism as an remarcable connection between diabetes and cardiovascular diseases.

Concluding Remarks

Endothelial dysfunction and more specifically, alteration in NO synthesis or action constitutes an essential step in the pathophysiology of most prevalent cardiovascular diseases. Due to essential NO functions (antiatherogenic, antithrombotic, antiproliferative agent), important changes are produced in the endothelial physiology when its biodisponibility is distorted. The multiple processes related to the reduction of synthesis and bioavailability of NO are far from being completely clarified. Although now days, a significant and growing body of information is being conformed, however, studies devoting to comprehension of biology of eNOS and its pathological modifications in the course of endothelial dysfunction are required. This fact will allow new pharmacological strategies generation in order to treat coronary heart disease since their beginnings, and consequently, preventing most feared complications in a safer and efficient approach.

References

1. Drexler H. Endothelial dysfunction: clinical implications. Prog Cardiovasc Dis. 1997; 39:287–324.
2. Boneti P, Lerman O, Lerman A. Endothelial Dysfunction: A Marker of Atherosclerotic Risk. Arterioscler Thromb Vasc Biol. 2003; 23:168-175.
3. O'Connell B, Genest J. High- Density Lipoproteins and Endothelial Function. Circulation. 2001; 104:1978-1983.
4. Kawashima S, Mitsuhiro Y. Dysfunction of Endothelial Nitric Oxide and Atherosclerosis. Arterioscler Thromb Vasc Biol. 2004; 24:998-1005.
5. Harrison D. Perspective Series: Nitric Oxide And Nitric Oxide Synthases. J. Clin. Invest. 1997; 100:2153-2157.

6. Govers R, Rabelink T. Cellular Regulation of Endothelial Nitric Oxide Synthase. Am J Pyshiol Renal Physiol. 2001; 280:193-206.
7. Palmer RM, Ashton DS, and Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature. 1988; 333:664–666.
8. Zembowicz A, Hecker M, Macarthur H, Sessa WC, and Vane JR. Nitric oxide and another potent vasodilator are formed from NG-hydroxy-L-arginine by cultured endothelial cells. Proc Natl Acad Sci USA. 1991; 88:11172–11176.
9. Abu-Soud HM and Stuehr DJ. Nitric oxide synthases reveal a role for calmodulin in controlling electron transfer. Proc Natl Acad Sci USA. 1993; 90:10769–10772.
10. Teichert AM, Miller TL, Tai SC, Wang Y, Bei X, Robb GB, Phillips MJ, and Marsden PA. In vivo expression profile of an endothelial nitric oxide synthase promoter-reporter transgene. Am J Physiol Heart Circ Physiol. 2000; 278:H1352–H1361.
11. Nishida K, Harrison DG, Navas JP, Fisher AA, Dockery SP, Uematsu M, Nerem RM, Alexander RW, and Murphy TJ. Molecular cloning and characterization of the constitutive bovine aortic endothelial cell nitric oxide synthase. J Clin Invest. 1992; 90:2092–2096.
12. Alonso J, Sanchez de Miguel L, Monton M, Casado S, and Lopez-Farre A. Endothelial cytosolic proteins bind to the 39 untranslated region of endothelial nitric oxide synthase mRNA: regulation by tumor necrosis factor alpha. Mol Cell Biol 1997; 17:5719–5726.
13. Lu JL, Schmiege LM, 3rd Kuo L, and Liao JC. Downregulation of endothelial constitutive nitric oxide synthase expression by lipopolysaccharide. Biochem Biophys Res Commun. 1996; 225:1–5.
14. McQuillan LP, Leung GK, Marsden PA, Kostyk SK, and Kourembanas S. Hypoxia inhibit expression of eNOS via transcriptional and posttranscriptional mechanisms. Am J Physiol Heart Circ Physiol. 1994; 267:1921–1927.
15. Liao JK, Shin WS, Lee WY, and Clark SL. Oxidized lowdensity lipoprotein decreases the expression of endothelial nitric oxide synthase. J Biol Chem.1995; 270:319–324.
16. Pou S, Pou WS, Bredt DS, Snyder SH, and Rosen GM. Generation of superoxide by purified brain nitric oxide synthase. J Biol Chem. 1992; 267:24173–24176.
17. Stroes E, Hijmering M, Vanzandvoort M, Wever R, Rabelink TJ, and Vanfaassen EE. Origin of superoxide production by endothelial nitric oxide synthase. FEBS Lett. 1998;438:161–164.
18. Vasquez-Vivar J, Kalyanaraman B, Martasek P, Hogg N, Masters BSS, Karoui H, Tordo P, and Pritchard KA. Superoxide generation by endothelial nitric oxide synthase: the influence of cofactors. Proc Natl Acad Sci USA.1998; 95:9220–9225.
19. Wever RMF, van Dam T, van Rijn HJ, de Groot F, and Rabelink TJ. Tetrahydrobiopterin regulates superoxide and nitric oxide generation by recombinant endothelial nitric oxide synthase. Biochem Biophys Res Commun. 1997; 37:340–344.
20. Kojima, S., S. Ona, I. Iizuka, T. Arai, H. Mori, and K. Kubota. Antioxidative activity of 5,6,7,8-tetrahydrobiopterin and its inhibitory effect on paraquat-induced cell toxicity in cultured rat hepatocytes. Free Rad. Res. 1995; 23:419–430.
21. Pieper, G.M. Acute amelioration of diabetic endothelial dysfunction with a derivative of the nitric oxide synthase cofactor, tetrahydrobiopterin. Cardiovasc. Pharmacol. 1997;29:8–15.
22. Stroes, E., J. Kastelein, F. Cosentino, W. Erkelens, R. Wever, H. Koomans, T. Luscher, and T. Rabelink. Tetrahydrobiopterin restores endothelial function in hypercholesterolemia. J. Clin. Invest. 1997; 99:41–46.
23. Vann LR, Payne SG, Edsall LC, Twitty S, Spiegel S, Milstien S. Involvement of sphingosine kinase in TNF-alpha-stimulated tetrahydrobiopterin biosynthesis in C6 glioma cells. J Biol Chem. 2002; 277:12649–12656.
24. Dulak J, Polus M, Guevara I, Polus A, Hartwich J, Dembinska-Kiec A. Regulation of inducible nitric oxide synthase (iNOS) and GTP cyclohydrolase I (GTP-CH I) gene expression by ox-LDL in rat vascular smooth muscle cells. J Physiol Pharmacol. 1997; 48:689–697.
25. Cosentino F, Patton S, d'Uscio LV, Werner ER, Werner-Felmayer G, Moreau P, Malinski T, Luscher TF. Tetrahydrobiopterin alters superoxide and nitric oxide release in prehypertensive rats. J Clin Invest. 1998; 101:1530–1537.
26. Stroes, E, Kastelein J, Cosentino F, Erkelens W, Wever R, Koomans H, Luscher T, and Rabelink Tetrahydrobiopterin restores endothelial function in hypercholesterolemia. J Clin Invest. 1997;99:41–46.
27. Setoguchi S, Mohri M, Shimokawa H, Takeshita A. Tetrahydrobiopterin improves endothelial dysfunction in coronary microcirculation in patients without epicardial coronary artery disease. J Am Coll Cardiol. 2001;38:493–498.
28. Heitzer T, Brockhoff C, Mayer B, Warnholtz A, Mollnau H, Henne S, Meinertz T, Munzel T. Tetrahydrobiopterin improves endothelium dependent vasodilation in chronic smokers : evidence for a dysfunctional nitric oxide synthase. Circ Res. 2000;86:E36–E41.
29. Vallance, P., Leone, A., Calver, A., Collier, J. & Moncada, S. (1992) Accumulation of an endogenous inhibitor of NO synthesis in chronic renal failure. Lancet 339:572-575.
30. Leiper JM, Santa Maria J, Chubb A, et al. Identification of two human dimethylarginine dimethylaminohydrolases with distinct tissue distributions and homology with microbial arginine deaminases. Biochem J. 1999; 343:209–14.
31. Cooke, J. P., Andon, N. A., Girerd, X. J., Hirsch, A. T. & Creager, M. A. (1991) Arginine restores cholinergic relaxation of hypercholesterolemic rabbit thoracic aorta. Circulation 83:1057-1062.[Abstract/Free Full Text]
32. Böger, R. H., Bode-Böger, S. M., Mügge, A., Kienke, S., Brandes, R., Dwenger, A. & Frölich, J. C. (1995) Supplementation of hypercholesterolaemic rabbits with L-arginine reduces the vascular release of superoxide anions and restores NO production. Atherosclerosis 117:273-284.[Medline]
33. Böger, R. H., Bode-Böger, S. M., Phivthong-ngam, L., Böhme, M., Brandes, R. P., Mügge, A. & Frölich, J. C. (1997) Dietary L-arginine slows the progression of atherosclerosis in cholesterol-fed rabbits—comparison with lovastatin. Circulation 96:1282-1290.[Abstract/Free Full Text]
34. Candipan, R. C., Wang, B. Y., Buitrago, R., Tsao, P. S. & Cooke, J. P. (1996) Regression or progression. Dependency on vascular nitric oxide. Arterioscler. Thromb. Vasc. Biol. 16:44-50.[Abstract/Free Full Text]
35. Tsao, P. S., Theilmeier, G., Singer, A. H., Leung, L. L. & Cooke, J. P. (1994) L-Arginine attenuates platelet reactivity in hypercholesterolemic rabbits. Arterioscler. Thromb. 14:1529-1533.
36. Böger, R. H., Bode-Böger, S. M., Kienke, S., Nafe, R., Stan, A. C. & Frölich, J. C. (1998) Dietary L-arginine decreases myointimal cell proliferation and vascular leukocyte accumulation in cholesterol-fed rabbits. Atherosclerosis 136:67-77.
37. Mügge, A. & Harrison, D. G. (1991) L-Arginine does not restore endothelial dysfunction in atherosclerotic rabbit aorta in vitro. Blood Vessels 28:354-357.
38. Clarke S. Protein methylation. Curr Opin Cell Biol. 1993; 5:977–983.
39. Buga, G.M., R. Singh, S. Pervin, N.E. Rogers, D.A. Schmitz, C.P. Jenkinson, S.D. Cederbaum, and L.J. Ignarro.. Arginase activity in endothelial cells: inhibition by NG-hydroxy-L-arginine during high-output NO production. Am. J. Physiol. 1996; 271:1988–1998.
40. Parton RG. Caveolae and caveolins. Curr Opin Cell Biol. 1996; 8:542–548. Smart EJ, Graf GA, McNiven MA, Sessa WC, Engelman JA, Scherer PE, Okamoto T, and Lisanti MP. Caveolins, liquid-ordered domains, and signal transduction. Mol Cell Biol. 1999; 19:7289–7304.
41. Ju H, Zou R, Venema VJ, and Venema RC. Direct interaction of endothelial nitric-oxide synthase and caveolin-1 inhibits synthase activity. J Biol Chem. 1997; 272:18522–18525.
42. Michel JB, Feron O, Sacks D, and Michel T. Reciprocal regulation of endothelial nitric-oxide synthase by Ca-calmodulin and caveolin. J Biol Chem. 1997; 272:15583–15586.
43. Blair A, Shaul PW, Yuhanna IS, Conrad PA, and Smart EJ. Oxidized low density lipoprotein displaces endothelial nitric-oxide synthase (eNOS) from plasmalemmal caveolae and impairs eNOS activation. J Biol Chem. 1999; 274:32512–32519.
44. Feron O, Dessy C, Desager JP, Balligand JL. Hydroxy-methylglutarylcoenzyme A reductase inhibition promotes endothelial nitric oxide synthase activation through a decrease in caveolin abundance. Circulation. 2001; 103:113–118.
45. Feron O, Dessy C, Moniotte S, Desager JP, Balligand JL. Hypercholesterolemia decreases nitric oxide production by promoting the interaction of caveolin and endothelial nitric oxide synthase. J Clin Invest. 1999; 103:897–905.
46. Hirata K, Akita H, Yokoyama M. Oxidized low density lipoprotein inhibits bradykinin-induced phosphoinositide hydrolysis in cultured bovine aortic endothelial cells. FEBS Lett. 1991; 287:181–184.
47. Inoue N, Hirata K, Yamada M, Hamamori Y, Matsuda Y, Akita H, Yokoyama M. Lysophosphatidylcholine inhibits bradykinin-induced phosphoinositide hydrolysis and calcium transients in cultured bovine aortic endothelial cells. Circ Res. 1992; 71:1410–1421.
48. Miwa Y, Hirata K, Kawashima S, Akita H, Yokoyama M. Lysophosphatidylcholine inhibits receptor-mediated Ca^{2+} mobilization in intact endothelial cells of rabbit aorta. Arterioscler Thromb Vasc Biol. 1997; 17:1561–1567.
49. Vallance P, Chan N. Endothelial function and nitric oxide: clinical relevance. Heart. 2001; 85:342-350.
50. Thomson, L., M. Trujillo, R. Telleri, and R. Radi. Kinetics of cytochromec oxidation by peroxynitrite: implications for superoxide measurements in nitric oxide-producing biological systems .Arch Biochem. Biophys.1995M; 319:491–497.
51. Heitzer, T., H. Just, and T. Munzel. Antioxidant vitamin C improves endothelial dysfunction in chronic smokers. Circulation. 1996; 94:6–9.
52. Ting, H.H., F.K. Timimi, K. Boles, S. Creager, P. Ganz, and M.A. Creager. Vitamin C acutely improves endothelium-dependent vasodilation in patients with non-insulin-dependent diabetes mellitus. Circulation. 1995.92(Suppl.1):1747. (Abstr.).
53. Solzbach, U., B. Hornig, M. Jeserich, and H. Just. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. Circulation.1997; 96:1513–1519.
54. Hironori Nakagami, Yasufumi Kaneda, Toshio Ogihara and Ryuichi Morishita. Endothelial Dysfunction in Hyperglycemia as a Trigger of Atherosclerosis. Current Diabetes Reviews, 2005, 1, 59-63.
55. Christian Rask-Madsen and George L King. Mechanisms of Disease: endothelial dysfunction in insulin resistance and diabetes. Nature Clinical Practice Endocrinology and Metabolism Jan 2007, Vol 3, 46-56.
56. Brett E. Fenster, Philip S. Tsao P and Stanley G. Rockson. Endothelial dysfunction: clinical strategies for treating oxidant stress. American Heart Journal. Volume 146, Issue 2 , August 2003, Pages 218-226

Calcio, hipertensión arterial y daño a órganos blancos: de la prevención a la regresión

Morr Igor - Morr Carlos. Universidad de Carabobo- Venezuela
igormorr@cantv.net

Recibido: 26/03/2007 *Aceptado: 04/05/2007*

Resumen

Alteraciones en el metabolismo de los electrolitos magnesio, potasio y calcio se han asociado como factores etiológicos en la hipertensión arterial sistémica, cardiopatía isquémica, insuficiencia cardíaca, ateroesclerosis, diabetes mellitus y arritmias cardiacas. Actualmente existen fuertes evidencias que involucran al ion calcio en la patogénesis de la enfermedad arterial hipertensiva.

En varios estudios clínicos se ha informado sobre el rol que juegan los medicamentos que bloquean los canales del calcio mejorando algunos elementos del continuo cardiovascular, tales como: la tolerancia a la glucosa, niveles bajos de insulina y su acción positiva en la estabilización de la placa de ateroma.

En este artículo nos proponemos revisar las alteraciones del metabolismo del calcio y su papel en la patogénesis de la hipertensión arterial. También abordaremos lo relacionado al efecto benéfico de algunos fármacos con propiedades calcio antagonistas en el tratamiento de la ateroesclerosis, más allá de su acción antihipertensiva.

Palabras Claves: Metabolismo del Calcio, Hiper-tensión Arterial Primaria, Bloqueantes de los Canales del calcio, Insulino Resistencia, Ateroesclerosis.

Abstract

Abnormalities in the metabolism of the electrolytes, magnesium, potassium, and calcium have been associated as etiologic factors in systemic hypertension, ischemic heart disease, congestive heart failure, atherosclerosis, diabetes mellitus and arrhythmia. An increasing body of evidence suggests a critical role of calcium metabolism in the pathogenesis of hypertensive disease.

Several studies have reported that long-acting calcium channel blockers can improve some elements of the continuum cardiovascular such as: glucose tolerance, lower insulin levels and potential effect in plaque-stabilization properties.

The propose of this article consist in review the alterations of metabolism of calcium and his role in the pathogenesis of hypertension. Also we will discuss on the potential beneficial role for a calcium antagonist in the treatment on atherosclerosis, beyond of the antihypertensive action.

Key Words: Calcium metabolism, primary hypertension, calcium channel blockers, atherosclerosis

Introducción

Tanto como los estados de deficiencias como las anormalidades en el metabolismo de los electrolitos magnesio, potasio y calcio, se han identificado como factores etiológicos en la hipertensión arterial sistémica, cardiopatía isquémica, insuficiencia cardiaca, ateroesclerosis, diabetes mellitus y arritmias cardiacas. La reposición de estos electrolitos y su suplementacion de estas sustancias en animales de experimentación ha demostrado efecto benéfico en el tratamiento y prevención de estas condiciones cardiovasculares[1].

Alteraciones en el metabolismo de los iones calcio (Ca^{2+}) y magnesio (Mg^{2+}) se han implicado en la patogénesis de la hipertensión arterial primaria. El influjo de Calcio a través de la membrana celular en las células de musculo liso y el los cardiomiocitos poseen un papel crucial en el control de la excitación celular, contracción y propagación del impulso eléctrico. Las concentraciones intracelulares de Calcio y Magnesio son controladas por enlaces reversibles a proteínas específicas[2,3,4].

Por otro lado, se han reportado varios estudios de ensayos clínicos que algunos de los bloqueantes de los canales del calcio de acción prolongada (BCCs) intervienen positivamente en la reversión de algunos aspectos del continuo cardiovascular. Entre estos se citan sus efectos benéficos en el síndrome de Resistencia a la in-

sulina, en la reversión del daño endotelial y prevención de su disfunción así como en su papel de estabilizador de la placa de ateroma responsable de los eventos trombocitos agudos[5].

Aquí revisaremos estas alteraciones del metabolismo del calcio y su papel protagónico en la génesis de la hipertensión arterial. También discutiremos aspectos relacionados con el mecanismo celular y molecular de la acción de medicamentos que bloguean los canales del calcio y su efecto en el tratamiento, estabilización y regresión de la ateroesclerosis.

Metabolismo del Calcio y la Enfermedad Hipertesniva

Fuertes evidencias sugieren que existe un papel crítico de las alteraciones del metabolismo del calcio en la patogénesis de la enfermedad hipertensiva. En este sentido, se señala que el flujo de calcio transmembrana es regulado por una bomba de calcio (calcio-magnesio- AT-Pasa), los canales de calcio transmembrana y los enlaces con la membrana celular. Se han reportado incremento del calcio, descenso del magnesio e incremento en la relación calcio/magnesio en membranas celulares y en linfocitos de pacientes con hipertensión arterial esencial[4].

Algunos investigadores han observado la existencia de disturbios complejos en el metabolismo del calcio en modelos animales, en culturas celulares y en pacientes con hipertensión arterial. Así, el papel del incremento de las concentraciones de Ca^{2+} libre en el desarrollo y patogénesis de la hipertensión primaria ha sido extensamente estudiada[5,6]. El aumento de las concentraciones del calcio libre encontrados en el citosol de las células de musculatura lisa vascular se ha identificado como el responsable de la hipercontractilidad vascular en la hipertensión arterial.

Didácticamente podemos abordar el papel del calcio en la patogénesis de la hipertensión arterial en 4 aspectos:

- La relación entre los niveles de calcio y la presión arterial (PA)
- El efecto de la dieta y de los suplementos de calcio en la presión arterial
- La excreción renal de calcio y los niveles de paratohormona sérica (PTH) en pacientes con hipertensión arterial.
- El papel desempañado por el ion calcio en la génesis de la ateroesclerosis

Calcio y la regulación de la Presión Arterial

La hipertensión arterial es más frecuente en presencia de hipercalcemia y muchos estudios han encontrado una relación directa entre los niveles de calcio sérico y los de PA[6]. Sin embargo, la relación entre calcio iónico sérico y PA no parece ser lo suficientemente fuerte para establecer una causalidad entre ambas.

Existen suficientes datos experimentales en los que se sugiere que el efecto vasoconstrictor estimulado por una elevación del calcio extracelular, esta mediado por una estimulación de la liberación de catecolaminas[7]. Los niveles de calcio libre ($[Ca^{2+}]i$) reflejan el estado de equilibrio entre el calcio extracelular y los depósitos de calcio intracelular: en la hipertensión arterial, los niveles elevados de calcio evidencian una alteración de por lo menso un de estos componentes (intra y extracelular) y se expresan de forma muy variable intra personal como interpersonal. Además este equilibrio es influenciado por la dieta, el volumen plasmático, las hormonas que regulan el calcio, las moléculas tipo ouabaina y factores dependientes de la paratiroides generadores de hipertensión arterial.

En las células de musculo liso vascular, la despolarización de la membrana plasmática-inducida por la corriente de Ca^{2+}- y la subsecuente liberación de Ca^{2+} desde el retículo sarcoplasmico, eleva los niveles de Ca^{2+} citosólico libre ($[Ca^{2+}]i$) y dispara una cascada de reacomodo molecular de calmodulina y miosina quinasa produciendo en última instancia acortamiento de los miofilamentos y la consecuente vasoconstricción. Contrariamente, en la vasorelajacion se reponen los niveles basales de $[Ca^{2+}]i$ por la vía de un incremento del eflujo de Ca^{2+} celular y una receptación del Ca^{2+} por parte del retículo sarcplasmico.

Los valores de PA se mantienen relativamente constantes mientras que el equilibrio de los niveles del $[Ca^{2+}]i$ permanezcan sin cambio. La homeostasis de la PA y del Ca^{2+} celular están regulados de forma coordinada a la manera de un "sube y baja".

Si el incremento continuo de Ca^{2+} extracelular a causa de una dieta rica en calcio, se detiene por una supresión igual y opuesta de angtiotensina II-dependiente hay liberación de $Ca^{2+\,i}$ intracelular, y la PA se mantiene constante. Por el contrario, en presencia de una dieta baja en sal, se produce un balance positivo de Ca^{2+} con un leve incremento transitorio del calcio iónico extracelular y un descenso fisiológico en las hormonas reguladoras del equilibrio del calcio. De esta forma la presión arterial se mantiene constante a menos de que exista un incremento del calcio extracelular o que una liberación del calcio intracelular exceda los límites fisiológicos de compensación. En condiciones como hiperaldosteronismo primario, hipertensión esencial de renina baja, estenosis unilateral de la arteria renal y en tumores secretores de renina se produce un desbalance que favorece la hipertensión arterial. Por otro lado en hipertensos de renina alta o normal, estenosis bilaterales de las arterias renales, pre-eclampsia, y tumores malignos se ha observado una falla en la supresión reciproca de los mecanismos contrareguladores[8].

Los hipertensos de renina baja presentan niveles bajos de calcio iónico y de calcitonina y recíprocamente niveles altos de magnesio, hormona paratiroidea (PTH) y de 1-25 dihidroxivitamina D (1,25D) cuando se compara con normotensos y otros subtipos de hipertensión. En los pacientes hipertensos con renina alta se observa todo lo contrario. (Tabla 1). Estas desviaciones en ambas direcciones de los valores normales sugieren une deficiencia de calcio extracelular en personas con reninas bajas y lo contrario en personas con reninas altas[9].

Table 1. Fisiopatología del Metabolismo del Calcio en la Hipertensión Arterial

Datos Epidemiologicos: relación HTA con ↓ de la ingesta de Ca2+ o del ↑del consumo de Mg 2+

P.A es proporcional a nivel de Ca2+ e inversamente proporcional a nivel de Mg 2+ (a nivel intracelular)

A nivel extracelular:
- Renina baja: ↓ del calcio iónico, calcitonina, ↑del Mg 2+, PTH, 1,25D.
- Renina Alta: ↑del calcio iónico, calcitonina, ↓del Mg 2+, PTH, 1,25D.

Hipertensión sensible a la sal: P.A. proporcional al 1,25D, Ca2+, inversamente proporcional al Mg 2+ y al calcio iónico.

1. Hunt SC, et al.Am J Hypetns.1991;4:1-8.

Los canales de calcio voltaje dependientes en la membrana plasmática son importantes para el influjo de calcio y para la contractilidad vascular; el bloqueo de estos canales con antagonistas como las Dihidropiridinas, Fenilalquilaminas y Benzodtizepinas favorecen y aumentan la relajación vascular. Esto tiene significancia clínica en el control de la presión arterial y en la modulación de los efectos negativos del metabolismo del calcio en el continuo cardiovascular.

Calcio y Resistencia a la Insulina

Los niveles de glucosa juegan un papel importante en la regulación de los iones intracelulares. Incrementos de la misma a nivel extracelular aumentan el calcio iónico y descienden los niveles de magnesio y por consiguiente puede afectar al tono vascular basal. Subsecuentemente, la insulina también estimula el flujo iónico, aumenta los iones libres de Mg^{2+} y Ca^{2+} a nivel vascular y en otros tejidos.

En individuos hipertensos esta acciones iónicas se relacionan proporcionalmente con las variaciones de los valores de electrolitos basales con respecto a los niveles normales. De esta forma la resistencia a la insulina debe considerarse, parcialmente, como un fenómeno iónico que forma parte de un patrón de respuesta celular a diferentes estímulos. Este patrón está presente en varias situaciones clínicas como la hipertensión arterial, resistencia a la insulina, obesidad, y en la diabetes mellitus tipo 2; todas estas condiciones forman parte de los elementos clínicos del síndrome metabólico[10].

La resistencia a la insulina y la hiperinsulinemia son factores que promueven la ateroesclerosis en obesos y en pacientes hipertensos. Estos pacientes pueden requerir terapia para la resistencia a la insulina, la cual debe influir en la toma de decisión de medicamentos adecuados seguros. Así, los calcio antagonistas han demostrado un efecto neutro y positivo en la sensibilidad a la insulina. La amlodipina por ejemplo ha evidenciado mejoría en los parámetros que evalúan la sensibilidad a la insulina en pacientes con hipertensión arterial esencial[11]. Ueshiba[12] demostró en un ensayo este efecto positivo en la resistencia insulinica así como un incremento en los niveles de Dehydroepiandrosterona (un andrógeno adrenal con acciones antiaterogénicas, anti obesidad y antidiabéticas) en pacientes hipertensos obesos tratados con amlodipina, manidipina y cildinipina.

Suplementos de calcio, sal y los cationes divalentes intracelulares

Existen muchos reportes de estudios observacionales de calcio e hipertensión arterial, demostrando la mayoría de ellos una relación inversa entre la ingesta de calco en la dieta y los niveles de presión arterial. Sin embargo, en ensayos clínicos controlados donde se evaluaron el uso de suplementos de calcio en la dieta (1-4gr por hasta 4 años de seguimiento), estos resultados han sido menos consistentes; solo se pudo encontrar una relación positiva entre calcio e hipertensión arterial en los dos tercios de estos estudio[13].

La justificación para el uso de suplementos de calcio en la dieta se basa en el supuesto que los niveles de Paratohormona (PTH) son elevados en respuesta a niveles bajos de calcio iónico, con la consecuente hipercalciuria observada en algunas formas de hipertensión arterial volumen dependiente.

El exceso de volumen y alto consumo de sal transitoriamente bajan los niveles de Ca^{2+}, incrementando los niveles de hormonas relacionadas con el calcio como la PTH en y la 1,25 Dihidroxivitamina D (1,25D), conjuntamente con otros factores. Las hormonas calcio activas, la captación de Ca^{2+} extracelular, favorecen la vasoconstricción y suprimen la liberación de la Renina por parte del riñón. En pacientes sensible a la sal, una sobrecarga de la misma reproduce iguales efectos que los observados en pacientes con renina baja, evidenciándose un descenso del calcio extracelular, incremento del calcio intracelular y por lo tanto elevación de la PA[14].

Sin embargo, en poblaciones no seleccionadas de pacientes hipertensos, los estudios no han demostrado esta relación entre los niveles de calcio y cifras tensiónales[15]. En contraste, estudios en embarazadas si se ha demostrado una relación entre el suplemento de calcio en la dieta y el descenso de los valores sistólicos y diastólicos de la presión arterial, así como un descenso en el riesgo de presentación de Pre eclampsia[15].

En resumen, en base a los datos disponibles no se puede recomendar el uso de suplementos de calcio de forma rutinaria como medida terapéutica para la prevención o control de la hipertensión arterial. En algunos casos individuales se podrían beneficiar de esta conducta, como en las embarazadas, ancianos y pacientes con renina baja; sin embargo no existen actualmente métodos de pesquisas para identificar que grupos de pacientes podrían seleccionarse para beneficiarse de esta terapia[16,17].

Excreción Renal de Calcio

Tanto en condiciones basales como durante una infusión de calcio, los hipertensos excretan mas calcio que las personas normales. Esto puede ser secundario a un la presencia de un incremento de la excreción urinaria de calcio secundaria a la expansión de volumen sanguíneo y la excreción urinaria incrementada del sodio. Alternativamente también se ha interpretado esta situación como un descenso en el enlace del calcio a las células renales. De cualquier forma, el mecanismo preciso no está bien dilucidado y se observa principalmente en las formas de hipertensión volumen-dependiente[18].

El papel del Calcio en la Ateroesclerosis

La ateroesclerosis es un proceso sistémico que se manifiesta clínicamente en todo el árbol arterial. El proceso inicial se relaciona con un daño inicial endotelial, y consecuentemente la expresión de un proceso inflamatorio

consecuente[19]. Este proceso se caracteriza por la acumulación de células mononucleares, migración y proliferación de células de la musculatura lisa y formación de la placa ateroesclerótica, rica en LDL colesterol. Un gran número de estos mecanismos se producen por una alteración de la homeostasis del calcio. Por otra parte se evidencia un marcado cambio en el transporte de calcio transmembrana en los vasos ateroescleróticos, proponiéndose que los calcio antagonistas puedan tener un papel en la progresión de esta enfermedad[21].

Esta hipótesis fue evaluada en dos ensayos clínicos: PREVENT y CAPARES[22,23]. En estos estudios se evaluaron los efectos de un calcio-antagonista dihidropiridinico, la amlodipina, en el desarrollo y progresión de la lesión ateroesclerótica en arterias coronarias y carotideas, en pacientes con enfermedad arterial coronaria documentada. Estos estudios concluyen que la amlodipina puede tener un efecto antiaterogenico directo como resultado de su acción dependiente del calcio y de sus efectos pleiotropicos como: actividad antioxidante [(24)], remodelado de la membrana celular de la musculatura lisa (CML)[25], inhibición y proliferación de la CML[26], inhibición de la apoptosis endotelial[27], liberación de oxido nítrico por incremento de su producción[28] y modulación de la expresión genética[29]. Estos resultados han despertado un marcado interés en la potencial acción de estabilización de la placa ateroesclerótica observada con el uso de estos calcioantagonistas lipofílicos.

Conclusiones

La hipertensión arterial, la resistencia a la insulina, la obesidad y la diabetes mellitus tipo II presentan un sustrato fisiopatologico común por la elevación del calcio libre citosólico y la reducción de los niveles de magnesio.

La presión arterial es determinada por la relación entre calcio extracelular e intracelular cuyo equilibrio mantiene los niveles presóricos constantes.

Existen factores moduladores como los niveles de renina, las hormonas relacionadas con el calcio (PTH y la 1-25 D), la calcitonina, entre otras.

Estos mecanismos operativos calcio dependientes predicen la respuesta de a presión arterial a los cambios dietéticos y la terapia con drogas antihipertensivas.

Referencias

1. Frishman, W; Cavusoglo, E. and Zonszein. Magnesium, Potassium, and Calcium as potential cardiovascular disease therapies in: Cardiovascular pharmacotherapeutics Fishman and Sonnenblick ed. Mc Graw Hill, 1998).
2. Durlach J: New trends in international magnesium research. Magnes Res 1992;5:1-4
3. Kisters K et al: Decreased cellular Mg++ concentrations in a subgroup of hypertensives.Membrane model for the pathogenesis of primary hypertension . Am J Hypert.1998;11:1390-1393
4. Kisters, K et al Increased Calcium and decreased Magnesium concentrations and an increased calcium/magnesium ratio in spontaneously hypertensive rats versus Wistar-Kyoto rats: relations to arteriosclerosis.. Am. J. Hypert. 2004;17:59-62.
5. Fogari R, et al: Effects of amlodipine-atorvastatin combinations on inflammation markers and insulin sensitivity in nomocholesterolemic obese hypertensive patients. Eur J Clin Pharmacol 2006;62:817-822
6. Bruschi G et al: Cytoplasmic free calcium is increased in the platelets of spontaneously hypertensive rats and essential hypertensive patients. Clin Sci 1985;68:179-184
7. Reanesnik L.M. The cellular ionic basis of hypertension and allied clinical conditions. Prog. Cardiovascular Dis.1999; 42: 1-22).
8. Hunt SC, Willians RR,Kuidda H. Different plasma ionized calcium correlations with blood pressure in high and low rennin normotensive adults in Utah. Am J Hypetns.1991;4:1-8.
9. Reanesnik L.M. The cellular ionic basis of hypertension and allied clinical conditions. Prog. Cardiovascular Dis.1999; 42: 1-22)
10. Ersoy C. et all: Effect of amlodipine on insulin resistance & tumor necrosis factor-alpha levels in hypertensive obese type 2 diabetic patients. Indian J Med Res 2004; 120:481-.488.
11. Virsaladze D. Wide Clinical Implementation of Insulin Resistance Syndrome? Met. Syndr. And Related Disorderes.2006. Vol. 4 n. 3: 165-171)
12. Ueshiba H, Miyachi Y. Effects of the long-acting calcium channel blockers, Amlodipine, Manidipine and Clinidipine on Steroid Hormones and Insulin resistance in Hypertensive Obese Patients. Internal Medicin 2004; 43: 561-565)
13. Resnik LM. The cellular ionic basis of hypertension and allied clinical conditions. Prog Cardiovasc Dis. 1999;42:1-22
14. Resnick L.M.Divalents Cations in Hypertension. In: Hypertension Primer. Isso, J. and Black, H, editors. 2003. American Heart Association.)
15. Atallah AN, Hofmeyr GJ, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems (Cochrane Review). In : The Crochane Library, Issue 1. Oxford: Update Software,2000MA)
16. National Cholesterol Education Program Adult Treatment Panel III Report. Circulation 2002; 106: 3145-3421
17. Guidelines for the management of arterial hypertension. European Society of Hypertension/European Society of Cardiology. J Hypertens.2003; 21: 1011-1053)
18. Hatton DC, Young EW, Bukoski RD, MacCarron DA: Calcium metabolism experimental genetic hypertension, in Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, diagnosis and Management. New York, Raven ress, 1995:1193-1211.
19. Mason R.: Mechanisms of Atherosclerotic Plaque Stabilization for a Lipophilic Calcium Antagonist Amlodipine. Am J Cardiol 2001;88 (suppl): 2m-6m
20. Henry PD. Atherosclerosis, calcium, and calcium antagonists. Circulation 1985;72:456-459
21. Hsueh WA, Anderson PW. Hypertension, the endothelial cell and the vascular complications of diabetes mellitus. Hypertension 1992;20:253-263
22. Pit B et al: Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. Circulation 2000;102:1503-1510
23. Jorgensen B et al: Restenosis and clinical outcomes in patients treated with amlodipine after angioplasty Amlodipine Restenosis Study (CAPARES).J. Am Coll Cardiol 2000;35:592-599
24. Mason RP et al. Mechanisms of plaque stabilization for the dihydropiridines calcium channel blocker amlodipine: review of the evidence. Atherosclerosis 2002;165:191-199
25. Tulenko et al.Cholesterol, calcium and atherosclerosis: is there a role for calcium channel blockers in atheroprotection?.Int J Cardiol 1997;62(suppl 2):55s-66s
26. McMurray HF, Chahwala SB. Amlodipine exerts a potent antimifrational effect on aortic smooth muscle cells in culture. J Cardiovasc Pharmacol 1992; 20(suppl):s54-s56
27. Masson RP.Cytoprotective properties of a long.acting cilium channel blocker: new mechanism of action(abstract)
28. Zhan C, Hintze TH. Amlodipine releases nitric oxide from canine coronary micro vessels: an unexpected mechanism of action of a calcium channel-blocking agent. Circulation1998;97:576-580
29. Roth M, et al. Ca 2+ Channel blockers modulate metabolism of collagens within the extracellular matrix. Proc Natl Acad Sci USA 1996;93:5478-5482

Treatment Resistant Hypertension

Dr. Peter Bolli, Ambulatory Internal Medicine Teaching Clinic
Suite 225, 80 King Street
St. Catharines (ON)
L2R 7G1. Canada
e-mail: pbolli@xenomix.com

Recibido: 23/01/2007 *Aceptado: 20/03/2007*

Abstract

Treatment resistant hypertension is defined as a blood pressure not achieving goal blood pressure (<140/90 mmHg) with a combination of three or more antihypertensive drugs. There are several causes for patients not responding to antihypertensive medication. One of the major reasons is non-compliance to the treatment often due to real or perceived side effects or due to a great number of medications and frequent dosing. Exogenous substances, most frequently, non-steroidal anti-inflammatory drugs, and, often not recognized, over-the-counter medications containing ephedrine or pseudo-ephedrine, can reduce the effect of antihypertensive drugs. Obesity and obstructive sleep apnea oppose antihypertensive drug effects by several mechanisms but predominantly by an increase in the activity of the sympathetic and renin-angiotensin-aldosterone systems. White coat hypertension as a cause of treatment resistance is suspected if there is no target organ damage or if the patients complain of symptoms of hypotension during antihypertensive treatment. Secondary forms of hypertension, although comprising only about 5% of patients with treatment resistant hypertension, are important to identify as they may represent a curable form of hypertension.

Key words: antihypertensive treatment, treatment resistance, refractory hypertension, secondary hypertension.

Treatment is directed at identifying and if possible, remove or treat the cause of treatment resistance. Multidisciplinary patient education, involving family members and/or pharmacist, is important to increase compliance and to deal with side effects. Patients' history usually reveals the presence of exogenous substances. White coat hypertension can be assessed by ambulatory blood pressure monitoring or home blood pressure measurement. Weight loss in obese patients and continuous positive airway pressure in patients with obstructive sleep apnea render them susceptible to antihypertensive treatment and lower blood pressure significantly. Secondary forms of hypertension are treated by removal or treatment of the underlying cause. A rational drug combination is important and should include a diuretic. Often, additional antihypertensive drugs have to be added to achieve blood pressure control.

Treatment-resistant or refractory hypertension is defined as a blood pressure not achieving a target systolic blood pressure below 140 mmHg or a diastolic blood pressure below 90 mmHg on a combination of three or more antihypertensive drugs. The purpose of defining treatment-resistant hypertension is to alert caregivers to search for and eliminate or treat possible causes that prevent an appropriate response to antihypertensive treatment. There are several causes for resistance to treatment and therefore the exact prevalence of treatment-

resistance is not known and may also vary greatly according to the type of the patient population studied, whether the prevalence was studied in the hypertensive population in a cross-sectional approach or in more specialized clinics. Results from antihypertensive treatment trials are more reliable since the aim of these studies often was to achieve a target blood pressure, usually a blood pressure below 140/90 mmHg. In one of the largest antihypertensive treatment studies, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the goal systolic blood pressure of less than 140 mmHg was not achieved in 33% and the goal diastolic pressure of less than 90 mmHg was not achieved in 8% receiving a combination of three or more antihypertensive drugs[1]. In the older hypertensive population attainment of systolic blood pressure goal represents a major problem[2]. Several causes, sometimes combined, can lead to resistance to antihypertensive treatment[3].

Lack of adherence to antihypertensive treatment.

Although this does not represent true resistance to treatment, it represents a major reason for lack of blood pressure control[4]. A Canadian study[5] revealed that 50% of patients do not refill their prescriptions after 41/2 years of treatment. Since it is difficult to assess a patient's adherence to treatment, the magnitude of this problem might, if anything, be even greater. There are many reasons for non-adherence including real or perceived side effects, multiple drugs and frequent dosing, as well as forgetfulness, particularly in the elderly, societal, cultural and financial aspects as well as lack of physician motivation to pursue attainment of goal blood pressure and to follow treatment recommendations[6].

Side effects (adverse reactions)

Side effects can be real or perceived and account for a major reason for failure to reach target blood pressure. To distinguish between real or perceived side effects can be difficult but certain characteristics can be helpful. Real side effects are usually typical for a particular drug or class of drugs while the symptoms related to perceived side effects often are the same or are similar for each drug and mostly are of a non-specific nature or are vague e.g. tiredness, "pain allover", "just not feeling well", nausea, "funny head", etc. An important reason for perceived side effects is anxiety[7] and the fear of ingesting a "chemical substance" which is enforced by the obligatory published number of side effects in the packet insert.

Exogenous substances, factors

A great number of exogenous substances or factors can lead to treatment resistance by opposing the antihypertensive drug effect. Table 1 summarizes the most frequent exogenous causes. Among the most frequent culprits are non-steroidal anti-inflammatory drugs[8]. Non-steroidal anti-inflammatory drugs oppose the action of antihypertensive drugs by raising the blood pressure through sodium and volume retention secondary to blockade of the renal vasodilatory prostaglandins[9]. Excessive alcohol intake raises blood pressure and leads to treatment resistance; the mechanism that lead to hypertension and treatment refractoriness are not well known[10]. Through its potent vasoconstrictor effect, cocaine can lead to severe hypertension often also causing stroke and myocardial infarction. Often overlooked, because of their over-the-counter availability, are nasal decongestants containing ephedrine or pseudo-ephedrine.

Table 1. Exogenous substances and factors that can lead to resistance to antihypertensive blood pressure lowering

Non-steroidal anti-inflammatory drugs
Cyclooxygenase-2 inhibitors
Corticosteroids, anabolic steroids
Oral contraceptives, sex hormones
Ephedrine, pseudoephedrine (nasal decongestants)
Alcohol
Stimulants (cocaine, amphetamine)
Erythropoietin and analogues
Calcineurin inhibitors (cyclosporin, tacrolimus)

Obesity

Obesity represents a major reason for lack of response to antihypertensive treatment and control of blood pressure[1,11,12]. That obesity can be the cause of resistance to antihypertensive treatment is supported by the observation that losing weight often lowers blood pressure and restores responsiveness to treatment. The mechanisms whereby obesity increases blood pressure are not well defined but are considered to include salt and water retention as well as stimulation of the sympathetic and renin-angiotensin-aldosterone systems.

White coat hypertension

The prevalence of white coat hypertension varies between studies and according to the blood pressure cut-off levels for the definition of white coat hypertension but may be as high as 20%[13]. Therefore, white coat hypertension has to be considered as a possible cause for treatment resistant hypertension. Symptoms of over-treatment (mainly postural hypotension) with increasing antihypertensive treatment as well as the absence of target organ damage may draw attention to the presence of white coat hypertension. The diagnosis is made by ambulatory or home blood pressure measurements and antihypertensive treatment will have to be guided by these out-of-office blood pressure measurements.

Pseudohypertension

The classical form of pseudohypertension is caused by extreme stiffness of the brachial artery and is diagnosed by using the Osler maneuver which implies that the radial artery is still palpable even if the blood pressure cuff is inflated above the systolic blood pressure[14]. Due to the stiffness of the larger arteries, these patients, mostly elderly, respond poorly to antihypertensive treatment A less classical but more frequent reason for pseudohypertension is the use of too small a cuff size particularly in obese patients[15].

Secondary forms of hypertension

Although secondary forms of hypertension comprise about 5% or less of all hypertensives, it is important to recognize and diagnose them because they may represent a curable form of hypertension. The most frequent forms of secondary hypertension are listed in table 2. Renal artery stenosis occurs more frequently in the elderly hypertensive patients due to the greater prevalence of atherosclerotic disease and respective lesions in the renal arteries are usually located at the ostium of the renal artery. Atherosclerotic lesions comprise about 90% with the remaining 10% presenting as fibromuscular dysplasia. Renal artery stenosis has to be suspected in patients with recurrent flash pulmonary edema due to sudden cardiac diastolic dysfunction. A reduced renal function with an increase in serum creatinine by more than 30% particularly following treatment with an ACE inhibitor or an angiotensin receptor blocker, points to the presence of bilateral renal artery stenosis. Often, serum potassium is low because of secondary hyperaldosteronism.

Table 2. Secondary forms of hypertension and some of their characteristcs

Renal parenchymal diseases Creatinine clearance, proteinuria, specific renal pathology, edema
Renovascular disease (renal artery stenosis) Recurrent pulmonary edema, abdominal bruit, hypokalemia, renal failure
Primary hyperaldosteronism Hypokalemia: spontaneous <3.5 mmol/L, on diuretic <3.0 mmol/L
Pheochromocytoma Paroxysmal headaches, palpitations, anxiety, diaphoresis
Cushings syndrome/disease Clinical presentation, elevated free cortisol, hypokalemia
Hyperparathyroidism Elevated serum calcium, parathyroid hormone, gastric/duodenal ulcer
Carcinoid syndrome Diarrhea, flushing, increased 5-hydroxyindolacetic acid excretion
Obstructive sleep apnea Typical sleep pattern, daytime sleepiness, often associated obesity
Coarctation of the aorta Blood pressure difference upper/lower extremities, typical bruit
Tumor of the central nervous system Specific neurological signs, hyponatremia

In patients with chronic kidney disease resistance to antihypertensive treatment is usually due to the absence of a diuretic in the antihypertensive drug combination or insufficient diuretic treatment since treatment resistance is mostly due to sodium and volume retention.

The prevalence of primary hyperaldosteronism has been reported as high as 20% in patients with treatment-resistant hypertension[16,17]. The clinical hallmark is a low serum potassium, below 3.5 mmol/L in patients who are not on a diuretic and below 3.0 mmol/L for those on a diuretic often with the associated symptoms, e.g. muscle weakness, cramps particularly during exercise due to the catecholamine-induced and beta-receptor-mediated intra-cellular movement of potassium.

A pheochromocytoma has to be suspected when the three cardinal symptoms, palpitations, headache, sudden episodes of anxiety are present with an attendant sudden rise in blood pressure and tachycardia[18].

Sleep apnea (apnea/hypopnea index of 10 events per hour or greater) probably represents the most frequent secondary cause of treatment-resistant hypertension[19,20,21]. The cause of the resistance to antihypertensive treatment in patients is not well known but includes an increase in sympathetic nervous system[22] and renin-angiotensin-aldosterone activity most likely due to frequent episodes of hypoxemia [23]. Increased urinary aldosterone excretion was found in patients with sleep apnea[24]. Because of the frequent combination of obesity and sleep apnea[25], both conditions may be responsible for the antihypertensive drug resistance and thus, it may be difficult to separate their respective contribution to the treatment resistance particularly as both conditions seem to use similar pathways to cause treatment resistance.

Coarctation of the aorta, Cushing disease, hypercalcemia, brain tumors and carcinoid syndrome are less frequently encountered but if present, can cause treatment resistant hypertension.

Treatment

The principal approach to the treatment of treatment resistant hypertension is to identify and eliminate the cause for treatment resistance. This requires the search for possible exogenous substances, including over the counter medications and herbal remedies and specific investigations to assess the possibility of a secondary form of hypertension. Adherence to medication can be improved by patient education preferably in multidisciplinary approach involving also family members and pharmacists. Simplification of treatment[26] e.g. once daily dosing, reduced number of pills through the use of combination

pills[27], and dated pill containers improve compliance particularly in elderly patients. To improve compliance in the case of perceived side effects can be difficult. First, the possibility that the side effects are caused by another, not the antihypertensive drug that the patient is taking has to be excluded as well as possible interactions. Patients often have a preconceived opinion that certain drugs are causing side effects. Again, patient education, sometimes in group sessions can eliminate the concerns of taking medication. Sometimes, the combination of several antihypertensive drugs, each given at a low ("sub-side effect") dose may be tolerated and blood pressure control be achieved.

Weight loss is paramount for obese patients to regain responsiveness to antihypertensive treatment. It has been shown, that a weight loss of 10 kg. lowers systolic blood pressure by 6 mmHg. and diastolic blood pressure by 4.6 mmHg.[28]. Cessation of excessive alcohol intake has been shown to reduce 24-hour ambulatory systolic pressure by 7.2 mmHg and diastolic pressure by 6.6 mmHg.[29]. In patients with sleep apnea, treatment with continuous positive airway pressure (CPAP) can restore responsiveness to antihypertensive treatment[30].

A rational combination of antihypertensive drugs is important and should include a diuretic since blood pressure lowering per se can lead to some sodium and volume retention which is often the cause for treatment resistance (table 3). In patients with chronic renal failure, the use of a loop diuretic may restore the responsiveness to antihypertensive treatment. Sometimes, centrally acting drugs e.g. clonidine or potent vasodilator drugs e.g. may have to be added in order to achieve treatment response through different additional modes of action. The addition of an aldosterone antagonist e.g. spironolactone[31] or eplerenone[32], a more selective aldosterone antagonis with fewer side effects as well as amiloride[33] has been found to cause an additional significant fall in blood pressure regardless of the plasma aldosterone or renin concentration or the amount of urinary aldosterone excretion[31] but requires the monitoring of serum potassium and renal function.

Table 3. Rational combination of antihypertensive drugs

Combination of: - Angiotensin converting inhibitor and/or angiotensin receptor blocker - Diuretic: thiazide diuretic loop diuretic if creatinine clearance <50ml/min or heart failure - Calcium channel blocker
Addition of: - Beta-blockers - Alpha-blockers (+beta –blocker combination) - Aldosterone antagonist (spironolactone, eplerenone, amiloride) - Clonidine - Hydralazine - Minoxidil - Methyldopa
Combination of a beta-blocker with a non-dihydropyridine calcium channel blocker should be avoided.
Monitoring of renal function and serum potassium in patients on an aldosterone antagonist and/or an angiotensin receptor blocker particularly in patients with diabetes or impaired renal function.
Avoid sudden discontinuation of clonidine (acute withdrawal syndrome) Minoxidil needs concomitant loop diuretic treatment (fluid retention)

References

1. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings; the Antihyperensive and Lipid- Lowering and Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens 2002 ;4:393-404.
2. Lloyd-Jones DM, Evans JC, Larsen MG, et al. Differential control of systolic and diastolic blood pressure : factors associated with lack of blood pressure control in the community. Hypertension 2000;36:594-599.
3. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med 2001;345:479-488.
4. Nuesch R, Schroeder K, Dieterle T, et al. Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: a prospective case-control study. BMJ 2001;323:142-146.
5. Caro JJ, Speckman JL, Salas M. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. CMAJ 1999;160:41-46.
6. Oliveria SA, Lapuerta P, McCarthy BD, et al. Physician-related barriers to the effective management of uncontrolled hypertension. Arch Intern Med 2002;162:387-388.
7. Davies SJ, Gharahmani P, Jackson PR, et al. Panic disorder, anxiety and depression in resistant hypertension: a case-control study. J Hypertens 1997;15:1077-1082.
8. Radack KI, Deck CC, Bloomfield SS. Ibuprofen interferes with the efficacy of antihypertensive drugs: a randomized, double-blind, placebo-controlled trial of ibuprofen compared with acetaminophen. Ann Intern Med 1987;107:628-635.
9. Fitzgerald GA. The choreography of cyclooxygenases in the kidney. J Clin Invest 2002;110:33-34.
10. de Gaudemaris R, Lang T, Chatellier G, et al. Socioeconomic inequalities in hypertension : prevalence and care : the IHPAF study. Hypertension 2002;39:1119-1125.
11. Kannel WB, Brand N, Skinner JJ Jr, et al. The relation of

to blood pressure and development of hypertension: the Framingham study. Ann Intern Med 1967;67:48-59.

12. Bramlage P, Pittrow D, Hans-Ulrich W, et al. Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. Am J Hypertens 2004;17:904-910.

13. Hermida RC, Ayala DE, Calvo C, et al. Effects of time of day of treatment on ambulatory blood pressure pattern of patients with resistant hypertension. Hypertension 2005;46:1053-1059.

14. Messerli FH, Ventura HO, Amodeo C. Osler's maneuvre and pseudohypertension. N Engl J Med 1985; 312:1548-1551.

15. Trout KW, Bertrand CA, Williams MH: Measurement of blood pressure in obese patients. JAMA 1956;162:970-971.

16. Calhoun DA, Nishizaka MK, Zaman MA, et al. High prevalence of primary aldosteronism among black and white subjects with resistant hypertension. Hypertension 2002;40:892-896.

17. Mosso L, Carvajal C, Gonzalez A, et al. Primary aldosteronism and hypertensive disease. Hypertension 2003;42:161-165.

18. Manger WM, Gifford RW Jr. Pheochromocytoma: diagnosis and treatment. J Clin Hypertens 2002;4:62-72.

19. Peppart PE, Young T, Palta M, et al. Prospective study of the association between sleep-disorderd breathing and hypertension. N Engl J Med 2000;342:1378-1384.

20. Nieto FJ, Young T, Lind BK, et al. for the Sleep Heart Health Study. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA 2000;283:1829-1836.

21. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnea in drug-resistant hypertension. J Hypertens 2001;19:2271-2277.

22. Esler M. The sympathetic system and hypertension. Am J Hypertens 2000;13:99S-105S.

23. Narkiewicz K, van de Borne PJ, Pesek CA, et al. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. Circulation 1999;99:1183-1189.

24. Calhoun DA, Nishizaka MK, Zaman MA, et al. Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea. Chest 2004;125:112-117.

25. Caples SM, Gami AS, Somers VK, et al. Obstructive sleep apnea. Ann Intern Med 2005;142:187-197.

26. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. Arch Intern Med 2004;164:722-732.

27. Materson BJ, Reda DJ, Cushman WC, et al. Results of combination anti-hypertensive therapy after failure of each of the components. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. J Human Hypertens 1995;9:791-796.

28. Aucott L, Poobalan A, Smith WC, et al. Effect of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review. Hypertension 2005;45:1035-1041.

29. Aguilera MT, de la Sierra A, Coca A, et al. effect of alcohol abstinence on blood pressure assessment by 24-hour ambulatory blood pressure monitoring. Hypertension 1999;33:653-657.

30. Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Ciirculation 2003;107:68-73.

31. Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low dose spironolactone in subjects with resistant hypertension. Am J Hypertens 2003;16:925-930.

32. Krum H, Nolly h, Workman D, et al. Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients. Hypertension 2002;40:117-1

33. Eide IK, Torjesen PA, Drolsum A, et al. Low renin status in therapy-resistant hypertension: a clue to efficient treatment. J Hypertens 2004;22:2217-2226.

Subclinical infection as cause of inflammation in preeclampsia

P. López-Jaramilloa,b, J.A. Herrera,
M. Arenas-Mantillaa, I.E. Jáureguia, M.A. Mendoza,
a VILANO GROUP, Research Institute, Cardiovascular Foundation of Colombia, Floridablanca, Santander, Colombia.
b Research Direction, Medical School, Universidad de Santander (UDES), Bucaramanga, Santander, Colombia.
c Department of Family Medicine, School of Medicine, Universidad del Valle, Cali, Valle del Cauca, Colombia.
Keywords: Preeclampsia, inflammation, infection, endothelium, nitric oxide Word count: Abstract: 216; Manuscript: 1482
Correspondence and request for reprints: Patricio López–Jaramillo, MD, PhD.
Instituto de Investigaciones, Fundación Cardiovascular de Colombia. Calle 155ª # 23-58, 3rd Floor.
Floridablanca, Santander, Colombia Tel: 577-6399292. Ext.331-343. Fax: 577-6392744.
E mail: joselopez@fcv.org, jplopezj@hotmail.com

Recibido: 22/02/2007 *Aceptado: 23/04/2007*

Abstract

Preeclampsia, a pregnancy-exclusive hypertensive disorder, is the major cause of maternal and perinatal mortality, with a greater importance in developing countries. The role of inflammation in the pathogenesis of preeclampsia has been the object of recent studies by our group. We have described elevated levels of inflammatory markers (TNFα, IL6 and CRP) in preeclamptic patients and demonstrated that Latin-American women present a higher degree of inflammation than women from developed countries. We have results that suggest that chronic subclinical infections and insulin resistance are the most probable causes of the increased inflammation in preeclampsia. Moreover, we showed that early treatment of urinary and vaginal infections decreased the incidence of preeclampsia. We also have evidences that suggest that inflammation leads to endothelial dysfunction, predisposing women to develop preeclampsia. Increased levels of inflammation markers and endothelial dysfunction are found in the early stages of pregnancy in women who later on develop preeclampsia. Appropriate prenatal care programs, including screening and treatment of urinary, vaginal and periodontal infections in early pregnancy and prevention of factors that predispose to insulin resistance, as excessive weight gain during pregnancy, may reduce the incidence of preeclampsia in Latin-American women.

Introduction

Hypertensive disorders during pregnancy are the principal cause of maternal and perinatal morbidity and mortality, preeclampsia (PE) being the most important among these alterations[1,2]. The etiology of PE comprises multiple risk factors[3,4], and we have proposed that the impact of each of them varies with the populations, with considerable differences between developed and developing countries[5]. In Latin-America, inappropriate nutrition, young maternal age and inadequate prenatal care programs, are important risk factors in the development of PE. In these countries, PE is the main cause of maternal mortality, which is 10 to 20 fold higher than in developed countries[2,5,6].

Excessive inflammation and risk of preeclampsia

Healthy pregnant women present a certain degree of inflammation, due in part to the activation of the immune system induced by the fetal allograft[7]. However, preeclamptic women have an excessive inflammatory response as demonstrated by increased concentrations of proinflammatory cytokines[8]. The role of these cytokines in normal pregnancy is not entirely understood. Some of them have been related to the mechanisms involved in the initiation and maintenance of gestation. For instance, TNF-α seems to regulate invasion and growth of the trophoblast into maternal spiral arteries[7]. However, women who

developed PE have significantly higher levels of TNF-α, IL2 and IL6[8,12].

In Andean population[13], we have confirmed the increased concentrations of proinflammatory cytokines in women with PE and demonstrated that our normal pregnant women have significantly higher concentrations of CRP, TNF-α and IL6, than those reported in studies conducted in pregnant women from developed countries[10,12,14].

The relationship of sub-clinical infection with preeclampsia

Asymptomatic bacteriuria is more frequently diagnosed in pregnant women with PE[15,16]. Various studies have described that urinary infection is associated with the development of preeclampsia, and that this association is more frequent among primigravidae women[17,18]. We have demonstrated that the early diagnosis and treatment of urinary and vaginal infections decreased the incidence of PE by 64 %[19].

Chronic subclinical infection appears as a factor that alters the endothelial production of nitric oxide (NO), substance which maintains a basal vessel dilator tone in the cardiovascular system[20,21]. An increased oxidative stress produced by infection impairs the bioactivity of NO and leads to endothelial dysfunction, event that is crucial in the development of PE[4,22]. In support of this view, PE-like manifestations have been induced in experimental models by blocking endothelial production of NO[20,23]. Moreover, in a randomized, double-blind, placebo controlled clinical trial, we included primigravidae women with family history of PE and abnormal Doppler ultrasound in uterine or arcuate arteries (diastolic notch). Women received daily elemental calcium and conjugated linoleic acid or lactose–starch placebo[24,25]. Endothelial function was evaluated by flow mediated dilation (FMD), method that has been validated in our population[26, 27]. Moreover, all women were screened for urinary and vaginal infections. The frequency of endothelial dysfunction was significantly higher among women with these infections and the antibiotic therapy improved FMD and decreased the risk of PE[24,25]. Recently, we established a cohort of 506 Colombian pregnant women with known risk factors for PE. FMD was realized in all women at 16 weeks of gestation and blood samples were withdrawn. All women were followed until delivery, 32 who developed PIH (Pregnancy induced hypertension) and 64 controls matched by body mass index and maternal and gestational age, were included in a nested case-control study[28]. CRP concentration and leukocyte counts were higher and FMD was lower in the women who developed PIH, suggesting that inflammation and endothelial dysfunction early in pregnancy precede the appearance of the clinical manifestations of PE. Furthermore, a correlation between the degree of inflammation and the severity of the hypertensive disorder was observed[28]. On the basis of these results we have suggested that inflammation secondary to chronic subclinical infection increases the risk of PIH[19].

Periodontal infection and risk of preeclampsia

Several studies have demonstrated a relationship between periodontitis and increased risk of PE, preterm delivery and low birth weight[29-31]. In Colombia we have reported[32] that chronic periodontal disease was more frequent in women with PE than in healthy pregnant controls (63.8% vs 36.6%), with a significant association between PE and chronic periodontitis (OR: 3.0; 95%-CI: 1.91-4.87). Two red complex microorganisms, Porphyromonas gingivalis and Tannerella forsythensis, and the green complex microorganism Eikenella corrodens were more frequently isolated in women with PE. These pathogens have also been isolated in atherosclerotic plaques in humans with coronary artery disease[33]. Moreover, we assessed the periodontal state and the CRP concentrations in 145 preeclamptic and 253 healthy pregnant controls[34]. Women with PE had a higher frequency of chronic periodontal disease (59% vs 36%; p<0.001) and in these women the CRP concentrations increased progressively depending on the severity of the periodontal disease. The CRP levels were significantly higher in the moderate/severe periodontitis group of women with PE [0.01]. Additionally P. gingivalis and E. corrodens were isolated more frequently in preeclamptic women[34]. These studies demonstrate a significant association between chronic periodontitis and PE, and suggest that the systemic inflammation observed in women that developed PE could be the result of periodontal infection.

Conclusión

Preeclampsia is the most important cause of maternal mortality in developing countries. Among the several conditions identified as risk factors for PE, sub-clinical infections have a major role in Latin-American population. Chronic inflammation induced by periodontal, vaginal and/or urinary infections causes endothelial dysfunction, a crucial alteration in the pathophysiology of PE. Early diagnosis and treatment of asymptomatic urinary and vaginal infections have been demonstrated to be an effective strategy to reduce the incidence of PE. Screening and treatment of common sub-clinical infections must be incorporated to the prenatal care programs, if we want to obtain a considerable reduction in maternal and perinatal mortality due to PE.

Acknowledgements

To the Colombian Institute for Science and Technology Development "Colciencias" (Grant No 6566-04-18061). The authors would like to thank Jean Noël Guillemot for his assistance in preparing the manuscript.

References

1. Walker JJ: Pre-eclampsia. Lancet 2000; 356:1260–1265.
2. Maternal mortality in 2000: estimates developed by WHO, UNICEF and UNFPA. World Health Organization 2004.
3. López-Jaramillo P: Calcium, nitric oxide, and preeclampsia. Sem Perinatol 2000; 24: 33-36.
4. López-Jaramillo P, Casas JP, Serrano NC: Preeclampsia: from epidemiological observations to molecular mechanisms. Braz J Med Biol Res 2001; 34: 1227-1235.
5. López-Jaramillo P, Garcia RG, López M: Preventing pregnancy-induced hypertension: are there regional differences for this global problem? J Hypertens 2005; 23: 1121-1129.
6. WHO. Technical Report Series. The hypertensive disorders of pregnancy. Geneva, 1987.
7. Kupferminc MJ, Peaceman AM, Wington TR, Tamura RK, Rehnberg KA, Socol ML: Inmunoreactive tumor necrosis factor-α is elevated in maternal plasma but undetected in amniotic fluid in the second trimester. Am J Obstet Gynecol 1994; 171: 976-979.
8. Redman C, Sacks G, Sargent I: Preeclampsia: An excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol 1990; 180: 499-506.
9. López-Jaramillo P, Escudero C, Moya W: Markers of systemic inflammation and nitric oxide metabolites in preeclampsia. Nitric Oxide Biol Chem 1998; 2: 127.
10. Vince GS, Starkey PM, Austgulen R: Interleukin-6, tumor necrosis factor and soluble receptors in women with preeclampsia. Br J Obstet Gynaecol 1995; 102: 20-25.
11. Hamai Y, Fujii T, Yamashita T, Nishina H, Kozuma S, Mikami Y, et al: Evidence for elevation in serum interleukin-2 and tumor necrosis factor-alpha levels before the clinical manifestations of preeclampsia. Am J Reprod Inmunol 1997; 38: 89-93.
12. Kupferminc MJ, Peaceman AM, Aderka D, Wallach D, Socol ML: Soluble tumor necrosis factor receptors and interleukin-6 levels in patients with severe preeclampsia. Obstet Gynecol 1996; 88: 420-427.
13. Teran E, Escudero C, Moya W, Flores M, Vallance P, López-Jaramillo P: Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with preeclampsia. Int J Gynecol Obstet. 2001; 75:243-249.
14. Greer IA, Lyall F, Perera T, Boswell F, Macara LM: Increased concentrations of cytokines interleukin-6 and interleukin-1 receptor antagonist in plasma of women with preeclampsia: a mechanism for endothelial dysfunction? Obstet Gynecol 1994; 84: 937-940.
15. Hill JA, Devoe L, Bryans C: Frequency of asymptomatic bacteriuria in preeclampsia. Obstet Gynecol 1986; 67: 529-532.
16. Abi Said D, Annegers JF, Combs-Cantrell D, Frankowski RF, Willmore LJ: Case-control study of the risk factors for preeclampsia. Am J Epidemiol 1995; 142: 437-441.
17. Hsu CD, Witter FR: Urogenital infection in preeclampsia. Int J Gynecol Obstet 1995; 49: 271-275.
18. Mittendorf R, Lain KY, Williams MA, Walker CK: Preeclampsia. A nested, case-control study for risk factors and their interactions. J Reprod Med 1996; 41: 491-496.
19. Herrera JA, Chaudhuri G, López-Jaramillo P: Is infection a major risk factor for preeclampsia? Medical Hypotheses 2001; 57: 393-397.
20. Yallampalli C, Garfield RE: Inhibition of nitric oxide synthesis in rats during pregnancy produces signs similar to those of preeclampsia. Am J Obstet Gynecol 1993; 169: 1316-1320.
21. Moncada S, Higgs EA, Hodson HF, Knowles RG, López-Jaramillo P, McCall T, et al: The L-arginine:nitric oxide pathway. J Cardiovasc Pharmacol 1991; 17(Suppl 3): S1-S9.
22. Davidge ST. Oxidative stress and altered endothelial cell function in preeclampsia. Semin Reprod Endocrinol 1998; 16: 65-73.
23. Belayet HM, Kanayama N, Kathun S, El Maradny E, Masui M, Tokunaga N, et al: Decreased renal and hepatic blood flow with preeclampsia-like histologic changes was obtained by stimulation of the celiac ganglion with LPS. Am J Perinatol 1998; 15: 109-114.
24. Herrera JA, Shahabuddin AK, Ersheng G, Wei Y, García RG, López-Jaramillo P: Calcium plus linoleic acid therapy for pregnancy-induced hypertension. Int J Gynecol Obstet 2005; 91: 221-227.
25. Herrera JA, Arevalo-Herrera M, Shahabuddin AK, Ersheng G, Herrera S, García RG, et al: Calcium and conjugated linoleic acid reduces pregnancy-induced hypertension and decreases intracellular calcium in lymphocytes. Am J Hypertens 2006; 19: 381-387.
26. Sierra-Laguado J, García RG, López-Jaramillo P: Flow-mediated dilation of the brachial artery in pregnancy. Int J Gynecol Obstet 2006; 93: 60-61.
27. Accini JL, Sotomayor A, Trujillo F, Barrera JG, Bautista L, López-Jaramillo P: Colombian study to assess the use of noninvasive determination of endothelium-mediated vasodilatation (CANDEV). Normal values and factors associated. Endothelium 2001; 8: 157-166.
28. García RG, Celedón J, Sierra-Laguado J, Alarcón MA, Luengas C, Silva F, et al: Raised C-reactive protein and impaired flow medi-

ated vasodilation precede the development of preeclampsia. Am J Hypertens 2007; 20:437-442.

29. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R, Beck J. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol. 1996;67:1103-1113.

30. Boggess KA, Lieff S, Murtha AP, Moss K, Beck J, Offenbacher S: Maternal periodontal disease is associated with an increased risk for preeclampsia. Obstet Gynecol 2003; 101: 227-231.

31. Canakci V, Canakci CF, Canakci H, Canakci E, Cicek Y, Ingec M, et al: Periodontal disease as a risk factor for pre-eclampsia: a case control study. Aust N Z J Obstet Gynaecol 2004; 44: 568-573.

32. Contreras A, Herrera JA, Soto JE, Arce RM, Jaramillo A, Botero JE: Periodontitis is associated with preeclampsia in pregnant women. J Periodontol 2006; 77: 182-188.

33. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ: Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000; 71: 1554-1560.

34. Herrera JA, Parra B, Herrera E, Botero JE, Arce RM, Contreras A, et el. Periodontal disease severity is related to high levels of C-reactive protein in Preeclampsia. J Hypertens 2007; in press.