DISCUSSION GÉNÉRALE

Contexte sociétal

Les premières causes de mortalité dans le monde sont les maladies cardiovasculaires ischémiques (maladies coronariennes et accidents vasculaires cérébraux principalement). Ces pathologies se développent massivement dans le cadre de troubles métaboliques associés à l'obésité, au syndrome métabolique et au diabète de type 2 (Fornoni et al., 2005). La prévalence de ces pathologies a fortement augmenté lors de ces dernières décennies, avec en cause une alimentation trop riche en lipides et en sucres ajoutés, et également une trop forte sédentarité des populations.

La modification de l'alimentation chez les populations des pays développés relève de différents facteurs sociaux-économiques qui dépassent notre propos. Cependant l'arrivée des fast food ainsi que l'augmentation de la consommation de plats industriels, peu coûteux et riches en acides gras saturés, participent à l'évolution de la prévalence de l'obésité et du syndrome métabolique (Chen et al., 2012 ; Mejova et al., 2015).

Une sensibilisation des populations au danger de ce type d'alimentation, pourrait limiter leur consommation et ainsi réduire les risques cardiovasculaires associés. Cette sensibilisation, commence par une meilleure compréhension des mécanismes d'action délétères, induits par les troubles métaboliques, liés à ces déséquilibres alimentaires, notamment sur la fonction vasculaire.

C'est pourquoi, au cours de nos différents travaux, nous avons tenté de comprendre comment la fonction vasculaire est impactée par différents désordres métaboliques au cours de stade précoces, favorisant ainsi une éventuelle intervention préventive avant l'installation de dommages irréversibles.

Cible biologique

L'intérêt scientifique est généralement porté sur la compréhension et l'explication de phénomènes responsables d'états pathologiques établis. Il semble pourtant nécessaire de tenter de comprendre l'apparition de désordres physiologiques chez des personnes asymptomatiques, afin de limiter le décours vers un état pathologie avancé.

Dans ce contexte, une partie de nos travaux s'est intéressé30372e aux effets de la consommation de boissons sucrées sur la fonction vasculaire chez les personnes saines. La consommation de produits contenant des sucres ajoutés, est courante dans l'alimentation moderne. En effet, nous pouvons en retrouver dans toutes les préparations industrielles, et

particulièrement dans les boissons de type sodas, boissons énergétiques, eaux aromatisées, et même les jus de fruits. Ces boissons créent un apport considérable de sucres ajoutés à notre organisme, bien au-delà des besoins nutritionnels quotidiens. C'est pourquoi, nous observons une forte corrélation entre l'augmentation de la consommation de ces boissons et l'augmentation de la prévalence de l'obésité (Malik et al., 2006).

Différentes études ont révélé les dangers de ces sucres, notamment leur effet addictif, par une étude comparant la dépendance de rongeurs à la cocaïne et au sucrose (Lenoir et al., 2007). Si les animaux ont dès le départ le choix entre les deux composants, ils vont préférer le sucrose à la cocaïne. De plus, lorsqu'ils présentent du sucrose à des rongeurs dépendants de la cocaïne depuis plusieurs semaines, les animaux vont orienter leur préférence, une fois encore vers le sucrose, malgré la forte dépendance que crée le stupéfiant. Ainsi, en plus du plaisir lié au goût sucré sur les papilles, la consommation de sucre provoquerait une addiction. Cependant, d'autres études sont nécessaires afin de mettre en lumière les connexions nerveuses potentiellement impliquées, et évaluer si cette addiction est liée à la notion de plaisir, ou si la molécule de glucose est capable d'enclencher des mécanismes cellulaires au niveau du cortex cérébral, qui modifieraient la sensibilité des individus à ce composé. Une autre étude intéressante a montré que la consommation excessive de sucre chez des rongeurs femelles en gestation, prédisposait leur fœtus à développer un syndrome métabolique (Saad et al., 2016). De plus, il semblerait que l'association de produits sucrés et riches en lipides, potentialise leur consommation réciproque (Ishomoto et al., 2013).

Ces boissons sucrées contiennent du saccharose, constitué de 45% de glucose et 55% de fructose. Le fructose, un sucre simple contenu principalement dans les fruits, participe à l'élévation de la production de triglycérides, et donc à l'accumulation de masse grasse lorsqu'il est consommé en forte quantité (Jurgens et al., 2005 ; Bantle et al., 2000). Tandis que le glucose agit de manière néfaste sur la fonction vasculaire, et participe d'avantage à l'installation de dysfonctions endothéliales (Ceriello et al., 1996 ; Lorenzi et al., 1986). Ainsi, au cours de notre étude portant sur l'impact vasculaire d'une hyperglycémie aigue, nous nous sommes particulièrement intéressés au rôle du glucose sur la fonction vasculaire.

L'altération de la fonction vasculaire s'apparente principalement à une dysfonction endothéliale, causée par un déséquilibre de production entre les agents vasoconstricteurs et vasodilatateurs. En effet, l'endothélium, qui pourrait bien être le plus important organe endocrine de l'organisme, libère différents agents responsables de la régulation de

l'homéostasie vasculaire, dont le NO qui joue un rôle prépondérant dans la relaxation endothélium-dépendante des vaisseaux. Ainsi, l'apparition de dysfonction endothéliale est généralement causée par une diminution de la biodisponibilité de NO, liée à une augmentation du stress oxydant (Rochette et al., 2013).

En plus d'être une source calorique importante, ces bombes sucrées modifient de manière transitoire la balance redox des cellules cibles de cette hyperglycémie. En effet comme nous l'avons décrit au cours ce travail de doctorat, et notamment dans une letter (Meziat et al., 2016) en réponse à deux commentaires réalisés sur notre méta-analyse (Loader et al., 2015), une forte concentration de glucose engendre une production excessive d'EOR qui entraînent une diminution de la biodisponibilité du NO. Ce phénomène est lié à une diminution du substrat de la eNOS, la L-arginine, essentielle à la production du gazotransmetteur. En effet, il a été démontré que l'hyperglycemie, *via* une forte production d'EOR, stimule l'expression d'ADMA et d'arginase, responsables de la dégradation de la L-arginine. Les EOR oxydent également le cofacteur essentiel de la eNOS, le BH_4 en BH_2, qui ne peut alors plus jouer son rôle essentiel dans le couplage entre le transfert d'électrons et la synthèse de NO. La eNOS devient alors une source potentielle d'EOR et participe à l'installation d'un stress oxydant. De plus, le NO est une molécule très réactive qui peut se coupler à l'anion superoxyde pour produire du peroxynitrite, un agent oxydant très puissant responsable de nombreux dégâts cellulaires irréversibles.

Ainsi, une hyperglycémie aigue causée, par exemple, par la consommation d'une boisson sucrée entraîne une altération de la fonction de relaxation liée à l'endothélium, en altérant la voie du NO. Cependant, ces altérations de la capacité de relaxation sont transitoires (Mah et al., 2012), et les mécanismes déterminant le rétablissement de la fonction endothéliale, et notamment du NO ne sont pas bien décrits. Nous pouvons émettre l'hypothèse que dans un premier temps, l'insuline permet de rétablir la glycémie, permettant ainsi de limiter la stimulation de production d'EOR au niveau de la paroi vasculaire. Et dans un second temps, les mécanismes antioxydants restaurent les désordres cellulaires causés par le stress oxydant, permettant ainsi de rétablir la voie de la eNOS et donc la capacité de relaxation endothéliale des vaisseaux.

Une capacité adaptative

Un élément intéressant qui ressort de l'ensemble de ces études, est la capacité de l'endothélium à s'adapter à différents types de stress, à court ou à long terme. En effet, les

dysfonctions endothéliales causées par un stress hyperglycémique aigu, sont transitoires, et donc rapidement rétablit grâce à des mécanismes adaptatifs. En l'occurrence, la capacité de captation du glucose plasmatique par les tissus insulino-sensibles permettant de réguler rapidement la glycémie, mais également les défenses antioxydantes de l'organisme qui permettent de rétablir le déséquilibre redox cellulaire. L'endothélium produit de nombreuses enzymes antioxydantes (SOD, Catalase, glutathione peroxydase), permettant de préserver, ou du moins de restaurer, la biodisponibilité du NO. Le retour rapide de la fonction de relaxation endothéliale permet d'augmenter le flux sanguin et donc l'apport de glucose aux muscles et aux tissus adipeux, favorisant ainsi la baisse de la glycémie.

La réponse adaptative à ce type de stress définit en partie l'état de santé de la fonction vasculaire. En effet, chez des personnes insulino-résistantes ou diabétiques, ces mécanismes adaptatifs sont délétères, les tissus de stockage sont moins sensibles à la stimulation de l'insuline, et les défenses antioxydantes sont dépassées par une trop forte production d'EOR, engendrant des altérations vasculaires permanentes qui participent à l'installation de l'athérosclérose. Cette pathologie vasculaire est caractérisée par une accumulation de processus pro-oxydants et pro-inflammatoires, qui favorisent l'adhésion leucocytaire et la prolifération des cellules musculaires lisses. La formation d'AGE favorise également ce processus athérosclérotique, dont la dangerosité dépend de la rupture de la plaque d'athérome, qui peut venir obstruer des artères, et ainsi aboutir à une ischémie.

C'est pourquoi, aujourd'hui, l'évaluation de la tolérance au glucose est réalisée par un test d'hyperglycémie postprandiale, qui reflète d'avantage la capacité de l'organisme à s'adapter à un stress aigu, grâce notamment, à l'action de l'endothélium. En effet, *via* l'action de l'insuline, l'endothélium participe à la régulation de la glycémie. La stimulation de la voie du NO responsable d'un relâchement artériel, entraîne une augmentation du flux sanguin, qui permet d'augmenter la surface d'échange entre les cellules endothéliales et les molécules circulantes, favorisant ainsi la captation du glucose.

La compréhension des mécanismes biologiques demande de prendre en compte le maximum d'éléments pouvant interagir sur le phénomène étudié. Ainsi, l'étude de la fonction vasculaire ne peut se faire sans la totalité des tissus qui composent et qui participent à la régulation de l'homéostasie vasculaire.

Le modèle de rat syndrome métabolique (SMet) caractérisé au cours de l'étude 2, en accord avec certaines observations faites sur des individus obèses ou SMet (Hugget et al.,

2004 ; Agapitov et al., 2008), ne présente pas d'hypertension artérielle malgré une activité importante du SNS, et une concentration élevée de catécholamines plasmatique. De manière intéressante, notre étude révèle que ce phénomène adaptatif serait lié à une suractivation de la eNOS par un mécanisme adrénergique, limitant ainsi l'augmentation du tonus vasculaire, et donc de la pression artérielle systémique. Ainsi, lors de phase précoce du développement du SMet, l'endothélium est capable de mettre en place des mécanismes compensatoires qui permettent de limiter les altérations liés aux désordres métaboliques induit par la pathologie.
Le SNS agit également au niveau du tissu adipeux. Il régule la capacité lipolytique des adipocytes grâce à des stimulations adrénergiques, *via* des récepteurs α-adrénergiques anti-lipolytiques, et des récepteurs β-adrénergiques lipolytiques. Le SNS agit également au niveau du phénotype des adipocytes, en réduisant notamment leur taille (Lee et al., 2013) et en stimulant le phénomène de « browning » au niveau des adipocytes beiges (Ye et al., 2013), via une activation des récepteurs β-adrénergiques. Cependant, ces phénomènes devront être plus clairement décrits par des études ultérieures.

Depuis quelques années, il apparait très clairement que le tissu adipeux périvasculaire, jusqu'alors ignoré, semble participer à la fonction biologique des vaisseaux. Il semble ainsi nécessaire de l'inclure dans l'évaluation des capacités d'adaptation vasculaire, au cours d'une phase d'installation de troubles métaboliques chroniques.

De manière intéressante, nos travaux révèlent qu'en présence de son PVAT, le muscle lisse de l'aorte de rats SMet est plus sensible au NO en comparaison aux rats Ctrl, alors que sans la présence du PVAT, la relaxation de l'artère NO-dépendante tend à être délétère. Plusieurs publications ont mis en évidence l'effet anti-contractile du PVAT sur des artères saines, par des mécanismes impliquant l'ouverture de canaux potassiques par des composés tels que le sulfure d'hydrogène (Wojcicka et al., 2010) ou bien le PAME (palmitic acid methyl ester) (Lee et al., 2011). D'autres travaux mettent en évidence que le PVAT pourrait stimuler la guanylate cyclase soluble par le peroxyde d'hydrogène (Gao et al., 2007). La majorité des équipes qui se sont intéressées à l'influence du PVAT sur la fonction vasculaire en condition pathologique ont utilisé des modèles d'animaux ou bien des tissus humains dans des états avancés d'obésité et/ou de diabète de type 2 (Virdis et al., 2014 ; Meijer et al., 2013 ; Ma et al., 2010 ; Galvez et al., 2006). Cependant, Gil Ortega et al. montrent sur des animaux soumis à un régime *high fat* court (8 semaines), une augmentation de la production de NO au

sein du PVAT-HF (Gil-Ortega et al., 2010). Ce phénomène semblerait expliqué par le rôle de la leptine.

Ainsi, lors de la phase précoce de l'installation de pathologie métabolique telle que l'obésité, le phénotype et le profil sécrétoire du PVAT semble se modifier afin de préserver la fonction de relaxation vasculaire. Nous pouvons imaginer que lors de cette phase d'adaptation, la masse du PVAT étant plus importante, les adipocytes ont potentiellement une capacité de production et de sécrétion plus élevée. Ainsi, une quantité plus importante d'agents tels que le PAME, l'H_2S, l'H_2O_2 ou la leptine, peuvent être libérés et stimuler d'avantage la relaxation artérielle, permettant ainsi de préserver le tonus artériel.

De plus, Soltis et Cassis, semblent montrer que le PVAT absorbe les catécholamines, limitant ainsi leur effet pro-contractile. Ceci pourrait expliquer l'absence d'hypertension artérielle chez certains sujets atteints d'obésité ou de syndrome métabolique, dont le PVAT plus épais, pourrait bloquer l'action des catécholamines (Soltis et al., 1991).

Pour mieux évaluer les effets propres des agents vasoactifs produits nous avons utilisé le secretome du PVAT de nos différents animaux. De manière très intéressante, lorsque l'on met en contact un PVAT de rat SMet a priori non délétère, avec une aorte saine, la capacité de relaxation de l'artère est altérée, et ce *via* un mécanisme a priori, stress oxydant dépendant. Ces résultats démontrent la capacité de l'artère, à s'adapter face à un stress chronique métabolique, et au-delà d'une adaptation endothéliale, on s'aperçoit que la première cible semble être le PVAT. Cette hypothèse est appuyée par la « brownisation » du tissu après les 15 semaines de régime HFS, qui semble témoigner d'une augmentation du métabolisme du tissu *via* une capacité thermogénique plus importante, permettant de transformer une plus grande quantité de substrat en énergie thermique. Malgré cette transformation phénotypique, les sécrétions du PVAT aortique de rat HFS sont délétères pour une artère saine, suggérant que la communication interne entre le PVAT et les tissus artériels est assez complexe, et que les mécanismes d'adaptation ne sont pas seulement liés à la transformation du PVAT. D'ailleurs, lorsque l'on utilise le sécrétome du PVAT Ctrl sur une artère Ctrl, la relaxation est diminuée de moitié par rapport à la capacité de relaxation de l'artère avec le PVAT laissé intact autour. L'isolation du sécrétome est essentielle à la compréhension des mécanismes impliqués dans l'effet vasoactif du PVAT sur la fonction vasculaire. Cependant la séparation des deux tissus peut altérer la communication. En effet, au niveau des petits vaisseaux, le PVAT s'imbrique dans le tissu artériel, mais la structure est plus complexe pour les gros vaisseaux, où l'adventice forme une barrière entre le tissu artériel et le PVAT. Pour

communiquer avec le tissu sous-jacent, le PVAT utilise le *vasa vasorum*, un complexe artériel composé de petites artérioles et de capillaires (Brown et al., 2014 ; Ahmed et al., 2004). Ainsi, la séparation du PVAT de son tissu artériel au niveau aortique par exemple, annihile les liens entre les composantes vasculaires, et peut limiter l'action de certaines substances vasoactives possédant une demi-vie limitée. L'utilisation de lits artériels perfusés, tel que le lit artériel mésentérique, pourrait être une bonne stratégie permettant d'évaluer la stimulation de l'endothélium ou du PVAT de manière plus spécifique, en préservant les liens entre les différents tissus.

La proximité du PVAT avec le tissu artériel, et sa capacité pro-oxydative et pro-inflammatoire, sont d'un grand intérêt pour la compréhension des mécanismes à l'origine de dysfonction vasculaires, et offrent un large panel d'explorations futures.

L'exercice : une stratégie intéressante pour lutter contre les désordres métaboliques quotidiens.

L'exercice physique est aujourd'hui reconnu pour ses capacités à prévenir et corriger l'apparition de certains états pathologiques (Pedersen et al., 2015). L'OMS a d'ailleurs mis au point en 2010, les *« Recommandations mondiales en matière d'activité physique pour la santé »* afin de préconiser une prévention primaire des maladies non-transmissibles par l'exercice physique sur l'ensemble des populations. On estime que l'inactivité serait responsable de 6 à 10% des décès liés à des pathologies cardiovasculaires (Lee et al., 2012). En effet, la sédentarité est un facteur de risque indépendant du développement d'altérations métaboliques ou cardiovasculaires (Hammer et al., 2012). Ainsi, l'exercice physique est une stratégie de prise en charge globale, très intéressante pour traiter/limiter les désordres métaboliques qui caractérisent le syndrome métabolique (Martin-Cordero et al., 2011 ; Golbidi et al., 2012). De plus, il est bien démontré aujourd'hui que la pratique régulière d'exercice physique entraîne des adaptations vasculaires bénéfiques qui limitent la rigidité artérielle et les dysfonctions endothéliales liées au vieillissement (Santos-Parker et al., 2014). Ces adaptations sont majoritairement associées à l'augmentation de la protection contre le stress oxydant et les phénomènes pro-inflammatoires, qui participent à la réduction de l'épaisseur de la paroi artérielle (Santos-Parker et al., 2014 ; Ashor et al., 2014). Ces améliorations de la fonction vasculaire sont également associées à une augmentation de la

capacité de relaxation des artères, grâce à une stimulation de la voie du NO (Maiorana et al., 2003).

En accord avec la littérature, nos travaux démontrent que l'exercice permet de protéger la fonction vasculaire en amont ou bien pendant l'installation de désordre métabolique. En effet, nous avons montré qu'un protocole d'entraînement modéré permet de limiter les effets néfastes d'un stress hyperglycémique aigue sur la fonction endothéliale. Nous ne pouvons pas parler ici de correction de l'effet délétère de l'hyperglycémie aigue, puisque ce stress altère significativement la relaxation endothélium-dépendante de nos animaux entraînés en comparaison à la réponse en normoglycémie. Cependant, l'exercice physique potentialise la réponse vasculaire, et la capacité de relaxation endothélium-dépendante est identique chez un animal sédentaire en condition de normoglycémie et un animal entraîné en hyperglycémie. Bien que les capacités de potentialisation des défenses antioxydantes de l'exercice physique sur la fonction vasculaire, ainsi que sur la voie du NO soient des mécanismes potentiellement explicatifs de ce phénomène, d'autres explorations doivent être menées pour le confirmer.

Une stratégie de prévention secondaire a été utilisée sur des animaux développant un syndrome métabolique. Chez ces animaux, l'exercice a permis d'améliorer la fonction vasculaire mais dans sa globalité, c'est-à-dire en prenant en compte l'implication vasoactive du PVAT. D'ailleurs, l'exercice dans ce modèle, semble impacter plus particulièrement le phénotype et le métabolisme du PVAT, plutôt que le tissu artériel (endothélium et muscle lisse vasculaire). Les effets de l'exercice physique sur le tissu adipeux sont aujourd'hui bien décrits, et montrent des effets bénéfiques principalement sur le tissu adipeux sous-cutané abdominal. Une étude menée sur des rats sains, n'a montré aucun impact de l'exercice sur la capacité vasoactive du PVAT, malgré une diminution de la masse de celui-ci dans le groupe de rat entrainé (Araujo et al., 2013). A notre connaissance, deux études seulement, menées par la même équipe, ont évalué ce phénomène en condition pathologique, chez des porcs atteints de dyslipidémie, mais ils ne montrent pas d'amélioration de la fonction coronarienne par l'exercice physique *via* le PVAT. Pourtant, la capacité de l'exercice physique à améliorer la fonction vasculaire, ainsi que le métabolisme et le phénotype du tissu adipeux, en font une stratégie préventive/thérapeutique de choix. Il semblerait intéressant d'étudier le tissu adipeux périvasculaire humain, prélevé chez des personnes obèses, après un protocole de réhabilitation par l'exercice physique. Ce nouvel acteur offre de nouvelles perspectives dans la compréhension de la fonction vasculaire, et pourrait constituer un lien intéressant entre l'obésité ou le syndrome métabolique, et le développement de complications vasculaires.

CONCLUSION GENERALE ET PERSPECTIVES

Ces travaux de doctorat ont permis de mettre en valeurs le rôle clé de la fonction endothéliale et du couple eNOS/Stress oxydant, dans l'adaptation de la réponse vasculaire à différents troubles de l'homéostasie, qu'ils soient métaboliques aigu (boisson sucrée) ou chronique (régime de type « Western »). En effet, dans nos travaux, nous avons pu mettre en avant qu'un simple stress hyperglycémique aigu peut avoir des conséquences fonctionnelles sur la vasomotricité endothélium-dépendante. Néanmoins, en nous appuyant sur la littérature abondante, rapportant des altérations vasculaires endothéliales persistantes chez les sujets souffrant de désordres métaboliques tels que le diabète de type 2 ou le syndrome métabolique, nous interprétons cette dysfonction endothéliale transitoire associée à l'hyperglycémie, comme un élément précurseur de l'installation d'une pathologie vasculaire chronique. Ceci, néanmoins, reste à démontrer. En effet, cette diminution de la réponse de l'endothélium au cours d'un stress aigu est observée sur quelques territoires seulement et pourrait finalement être un élément adaptatif permettant une meilleure distribution sanguine à d'autres territoires corporels, tel que la circulation splanchnique. Il semble donc hâtif de conclure de manière définitive, sur le lien entre cette diminution de la fonction endothéliale au cours d'un stress hyperglycémique, et l'installation d'une pathologie vasculaire persistante. De nouveaux travaux, visant à multiplier ce type de stress et d'en observer les conséquences progressives sur la fonction vasculaire, semblent essentiels afin de pouvoir tirer des conclusions plus fines.

Il ne semble donc pas évident que la fonction vasculaire soit dangereusement impactée par ce type de stress. En effet, comme nous avons pu le montrer dans les études n°2 et n°3, celle-ci possède une forte capacité d'adaptation, lui permettant, même face à un stress récurent (régime High Fat High Sucrose) de mettre en place un certain nombre de mécanismes régulateurs, aboutissant à une normalisation de ses capacités de réponses physiologiques. Ainsi, dans l'étude n°2, une amélioration de l'activation de la eNOS à un stress adrénergique semble pouvoir réguler la pression artérielle en dépit de l'hyperactivation sympathique. Dans l'étude n°3, une bio-communication qui reste à élucider entre le PVAT et la musculature lisse du vaisseau, semble contribuer à une amélioration de la sensibilité au NO et ainsi à un maintien des capacités vasomotrices artérielles, en dépit de l'apparition d'une légère dysfonction endothéliale. Une des limites de ce travail de doctorat, est clairement que notre modèle de rat nourrit avec un régime HFS n'a développé qu'un état peu avancé de la pathologie métabolique. Néanmoins, ce qui peut être considéré comme une limite, nous a aussi permis d'étudier des phénomènes physiologiques ne pouvant être observés que dans la

phase précoce de ce type de maladie, et ainsi faire apparaitre un certain nombre de mécanismes de compensation, que nous n'aurions certainement pas pu observer à un stade plus avancé. Néanmoins, si ceci semble évident au regard de la littérature scientifique, ces hypothèses doivent être confirmées expérimentalement.

Un élément essentiel de ce travail a aussi été de confirmer le rôle relativement protecteur de l'exercice physique. Comme déjà largement décrit dans la littérature, celui-ci semble pouvoir agir sur le bon fonctionnement du système cardiovasculaire, notamment *via* son action sur l'endothélium artériel et la biodisponibilité du NO. Dans ce travail, nous avons apporté un nouvel élément, en montrant que l'exercice est non seulement capable d'impacter la voie de la eNOS au niveau de l'endothélium vasculaire, mais aussi au niveau du PVAT. Par ailleurs, il semble, à partir de notre travail, que le PVAT puisse aussi constituer une cible privilégiée des effets bénéfiques de l'exercice sur l'homéostasie vasculaire. Cependant, comment le PVAT communique avec l'endothélium artériel et avec le reste du vaisseau, demeure néanmoins une zone d'ombre.

Ainsi, pour conclure, bien que la découverte du rôle de l'endothélium artériel dans la régulation de la fonction vasculaire ne soit pas très récente (Zalthen et al., 1978), la complexité de son rôle et de son impact sur la santé cardiovasculaire, le maintiennent en première ligne dans la compréhension, la modulation et le traitement potentiel de nombreuses maladies cardiovasculaires. La découverte plus récente et moins documentée de son interaction potentielle avec le PVAT, ajoute encore un peu de complexité au schéma de départ. Cependant, ce PVAT contribu à mieux comprendre le fonctionnement de l'endothélium vasculaire, et apparait comme une potentielle nouvelle cible thérapeutique.

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ANNEXES

Acute Hyperglycemia Impairs Vascular Function in Healthy and Cardiometabolic Diseased Subjects: Systematic Review and Meta-Analysis

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Acute Hyperglycemia Impairs Vascular Function in Healthy and Cardiometabolic Diseased Subjects

Systematic Review and Meta-Analysis

Jordan Loader, David Montero, Christian Lorenzen, Rani Watts, Cindy Méziat, Cyril Reboul, Simon Stewart, Guillaume Walther

Objectives—Controversy exists over the effect of acute hyperglycemia on vascular function. In this systematic review, we compared the effect of acute hyperglycemia on endothelial and vascular smooth muscle functions across healthy and cardiometabolic diseased subjects.

Approach and Results—A systematic search of MEDLINE, EMBASE, and Web of Science from inception until July 2014 identified articles evaluating endothelial or vascular smooth muscle function during acute hyperglycemia and normoglycemia. Meta-analyses compared the standardized mean difference (SMD) in endothelial and vascular smooth muscle functions between acute hyperglycemia and normoglycemia. Subgroup analyses and metaregression identified sources of heterogeneity. Thirty-nine articles (525 healthy and 540 cardiometabolic subjects) were analyzed. Endothelial function was decreased (39 studies; n=1065; SMD, −1.25; 95% confidence interval, −1.52 to −0.98; $P<0.01$), whereas vascular smooth muscle function was preserved (6 studies; n=144; SMD, −0.07; 95% confidence interval, −0.30 to 0.16; $P=0.55$) during acute hyperglycemia compared with normoglycemia. Significant heterogeneity was detected among endothelial function studies ($P<0.01$). A subgroup analysis revealed that endothelial function was decreased in the macrocirculation (30 studies; n=884; SMD, −1.40; 95% confidence interval, −1.68 to −1.12; $P<0.01$) but not in the microcirculation (9 studies; n=181; SMD, −0.63; 95% confidence interval, −1.36 to 0.11; $P=0.09$). Similar results were observed according to health status. Macrovascular endothelial function was inversely associated with age, blood pressure, and low-density lipoprotein cholesterol and was positively associated with the postocclusion interval of vascular assessment.

Conclusions—To our knowledge, this is the first systematic review and meta-analysis of its kind. In healthy and diseased subjects, we found evidence for macrovascular but not microvascular endothelial dysfunction during acute hyperglycemia. **(*Arterioscler Thromb Vasc Biol*. 2015;35:2060-2072. DOI: 10.1161/ATVBAHA.115.305530.)**

Key Words: cardiovascular diseases ■ hyperglycemia ■ meta-analysis ■ microcirculation ■ nitric oxide ■ vascular

The prevalence of type 2 diabetes mellitus represents a major public health issue, directly affecting an estimated 312 million people worldwide.[1] This burden is projected to worsen due, in part, to increasingly sedentary lifestyles and unhealthy dietary habits predominantly characterized by an excess consumption of added sugars.[2–4] Habitual consumption of added sugars, most commonly in the form of sugar-sweetened beverages, is strongly associated with an increased risk in developing type 2 diabetes mellitus, as well as metabolic syndrome and obesity.[5–8] In addition, consumption of added sugars has been linked to an increased risk of developing cardiovascular disease (CVD), which is the leading cause of mortality among those with cardiometabolic disease.[1,9,10] Consumption of excess added sugars leads to acute hyperglycemia, which is considered a better predictor of future CVD events than fasting glycemia in healthy and diabetic populations.[11,12] Indeed, such acute hyperglycemic stress has also been proposed to contribute to vascular dysfunction,[13] which represents one of the main precursors to CVD.[14]

In normal vascular function, the endothelium and vascular smooth muscle (VSM) cells continuously interact to regulate vasodilation and vasoconstriction, maintaining optimal organ perfusion and vascular tone.[15,16] During acute hyperglycemia, increased oxidative stress has been proposed as a key trigger of vascular dysfunction by reducing nitric oxide (NO) production or NO bioavailability.[15,17,18] Furthermore, animal and

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Nonstandard Abbreviations and Acronyms	
CI	confidence interval
CVD	cardiovascular disease
NO	nitric oxide
SMD	standardized mean difference
VSM	vascular smooth muscle

in vitro studies suggest that acute hyperglycemia may also impair VSM function by disrupting VSM cell apoptosis, causing subsequent VSM cell proliferation and desensitization to NO.[19–21] However, whether endothelial and VSM functions are transiently impaired during acute hyperglycemia in humans is unclear because of discrepant results. Given this, we conducted a systematic review and meta-analysis of available studies comparing endothelial function alone or in combination with VSM function during acute hyperglycemia in healthy and cardiometabolic diseased individuals. To our knowledge, this represents the first systematic review and meta-analysis to assess the effect of acute hyperglycemia on vascular function.

Materials and Methods

Materials and methods are available in the online-only Data Supplement.

Results

Study Selection and Characteristics

A flowchart of study selection is shown in Figure 1. The systematic search resulted in the inclusion of 39 from 394 potential articles.[22–60] Fourteen of these articles reported vascular data for multiple subgroups of a given or diverse health status; thus, they were assessed as individual studies.[22,25–28,31,37,38,45,52,56–59] The main characteristics and clinical data for these studies are shown in Tables 1 and 2, respectively. Three potentially relevant studies were not available for full text reading and thus could not be included.[61–63] All studies assessed endothelial or VSM function during acute hyperglycemia and normoglycemia in a total of 1065 individuals classified as healthy (n=525), obese (n=72), impaired glucose tolerance (n=104), type 2 diabetes mellitus (n=229), hypertensive (n=94), metabolic syndrome (n=30), or type 1 diabetic mellitus (n=11).

Quality Assessment and Potential Bias

The quality of the studies was moderate-to-high. The mean score was 9.4±1.5 of possible 12 points (Table 1). The quality of evidence for outcomes demonstrating the effect of acute hyperglycemia on vascular function was low-to-moderate (Table 3). As for the evaluation of potential bias, the funnel plot (Figure 2), Begg and Mazumdar rank correlation test, and the Egger regression test suggested the presence of publication bias or other biases for the standardized mean difference (SMD) in endothelial function in the studies included in the meta-analysis (P<0.01 and P<0.01, respectively). There was no evidence of publication or other biases when assessing the SMD in VSM function in the studies included in the meta-analysis.

Endothelial Function

After data pooling, endothelial function was significantly decreased during acute hyperglycemia compared with normoglycemia (39 studies; n=1065; SMD, −1.25; 95% confidence interval [CI], −1.52 to −0.98; P<0.01; Figure 3). There was no difference between health groups in the SMD in endothelial function (P=0.13), but significant heterogeneity was detected (I^2=87%; P<0.01). Subgroup analysis of the SMD in endothelial function revealed that macrovascular function was significantly decreased during acute hyperglycemia compared with normoglycemia (30 studies; n=884; SMD, −1.40; 95% CI, −1.68 to −1.12; P<0.01), whereas no significant decrease was found in the studies that assessed microvascular endothelial function (9 studies; n=181; SMD, −0.63; 95% CI, −1.36 to 0.11; P=0.09). Heterogeneity was detected in the SMD in endothelial function for both macrovascular (I^2=84%; P<0.01) and microvascular function studies (I^2=90%; P<0.01). Of note, the heterogeneity about microvascular endothelial function was primarily explained (≈40%) by a single study,[30] and the exclusion of such study did not significantly alter the pooled effect size (8 studies; n=147; SMD, −0.18; 95% CI, −0.53 to 0.17; P=0.30).

VSM Function

After data pooling, VSM function was preserved during acute hyperglycemia versus normoglycemia (6 studies; n=144; SMD, −0.07; 95% CI, −0.30 to 0.16; P=0.55; Figure 4). There was no significant difference between health groups in the SMD in VSM function (P=0.49), and no heterogeneity was observed (I^2=0%; P=0.85). Because of limited data availability, it was not possible to analyze macro-VSM and micro-VSM function separately.

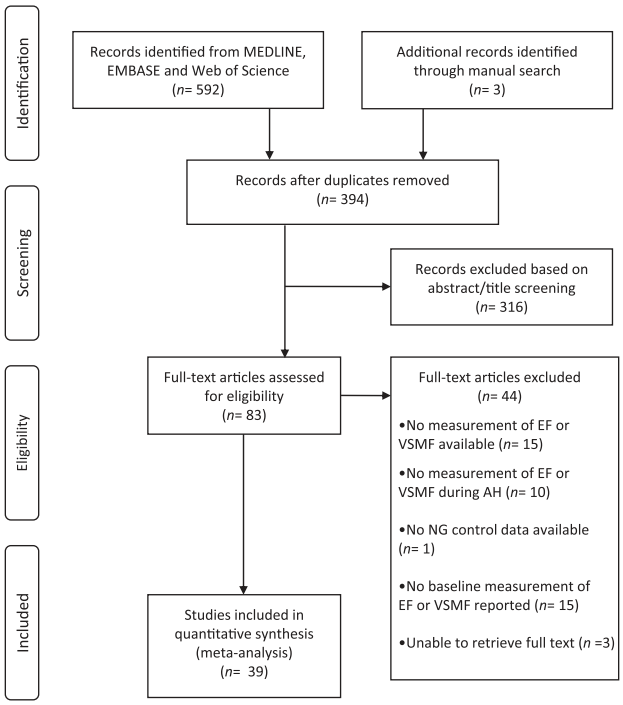

Figure 1. Flow diagram of the study selection process. AH indicates acute hyperglycemia; EF, endothelial function; NG, normoglycemia; and VSMF, vascular smooth muscle function.

Table 1. Main Characteristics of Studies Included in the Meta-Analysis

Study, Year of Publication	Study Design	Health Status	Medication	Quality Score (0–12)	Vascular Region	Inducing AH		Vascular EF During AH	VSMF During AH
						Method	Dose		
Grasser et al,[34] 2014	RCT	Healthy	None	9	Micro	Energy drink	Sucrose/ glucose, 39.1 g	↑ ACh	NA
Nakayama et al,[43] 2013	OBS	Healthy	None	6	Macro	Sugar drink	Maltose, 75 g	↓ FMD	NA
Mah et al,[42] 2013	RCT	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Wang et al A,[52] 2013	RCT	Healthy	None	9	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Zhang et al A,[59] 2013	RCT	Healthy	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
De Marchi et al,[30] 2012	RCT	Healthy	None	8	Micro	OGTT	Glucose, 75 g	↓ ACh	↔ SNP
Grassi et al,[35] 2012	RCT	Healthy	None	9	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Suzuki et al,[49] 2012	OBS	Healthy	None	8	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Ceriello et al A,[28] 2011	RCT	Healthy	None	6	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Mah et al,[41] 2011	RCT	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Watanabe et al,[53] 2011	OBS	Healthy	None	11	Macro	OGTT	Glucose 75 g	↓ FMD	NA
Baynard et al A,[25] 2009	OBS	Healthy	3 statin, 1 hydrochlorothiazide, 1 angiotensin II receptor blocker, 1 ACE inhibitor	9	Macro	Test meal	Carbohydrate, 80 g	↓ FMD	NA
Ceriello et al (1) A,[27] 2008	OBS	Healthy	None	8	Macro	IV infusion	Glucose, 15 mmol/L	↓ FMD	NA
Ceriello et al (2) A,[26] 2008	RCT	Healthy	None	8	Macro	IV infusion	Glucose, 15 mmol/L	↓ FMD	NA
Natali et al A,[45] 2008	OBS	Healthy	Unknown	11	Micro	OGTT	Glucose, 75 g	↔ ACh	↓ SNP
Weiss et al,[54] 2008	RCT	Healthy	None	10	Macro	Candy/sugar drink	Carbohydrate, 101 g	↓ FMD	NA
Xiang et al (1) A,[57] 2008	RCT	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↔ FMD	NA
Xiang et al (2) A,[56] 2008	OBS	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	↔ NMD
Xiang et al (2) B,[56] 2008	OBS	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↔ FMD	↔ NMD
Dengel et al A,[31] 2007	OBS	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↑ FMD	NA
Zhu et al,[60] 2007	RCT	Healthy	None	7	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Arora et al A,[22] 2006	OBS	Healthy	None	10	Micro	OGTT	Glucose 75 g	↓ PORH	NA
Fujimoto et al,[33] 2006	OBS	Healthy	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Tushuizen et al,[51] 2006	RCT	Healthy	None	11	Macro	Test meal	Carbohydrate, 55 g	↓ FMD	NA
Napoli et al,[44] 2004	RCT	Healthy	None	6	Micro	Test meal	Carbohydrate, 60 g	↔ ACh	↔ SNP
Siafarikas et al,[47] 2004	RCT	Healthy	None	9	Macro	OGTT	Glucose, 75 g	↔ FMD	NA
Ihlemann et al,[36] 2003	RCT	Healthy	None	7	Micro	OGTT	Glucose, 75 g	↓ Serotonin	↓ SNP
Bagg et al,[23] 2000	RCT	Healthy	None	9	Macro	IV infusion	Dextrose, 10% 238 mL	↔ FMD	NA
Title et al,[50] 2000	RCT	Healthy	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Kawano et al A,[38] 1999	OBS	Healthy	None	10	Macro	OGTT	Glucose, 75 g	↔ FMD	NA
Williams et al,[55] 1998	OBS	Healthy	None	10	Micro	IV infusion	Glucose, 16.7 mmol/L	↔ Metacholine	NA
Lavi et al,[40] 2009	RCT	Obese	None	8	Macro	Sugar drink	Glucose, 50 g	↓ FMD	NA
Dengel et al B,[31] 2007	OBS	Obese	None	11	Macro	OGTT	Glucose, 75 g	↑ FMD	NA
Wang et al B,[52] 2013	RCT	IGT	None	9	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Natali et al B,[45] 2008	OBS	IGT	Unknown	11	Micro	OGTT	Glucose, 75 g	↔ ACh	↓ SNP
Xiang et al (1) B,[57] 2008	RCT	IGT	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Arora et al B,[22] 2006	OBS	IGT	None	10	Micro	OGTT	Glucose, 75 g	↓ PORH	NA
Kawano et al B,[38] 1999	OBS	IGT	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Wang et al C,[52] 2013	RCT	T2DM	None	9	Macro	OGTT	Glucose 75 g	↓ FMD	NA

(*Continued*)

Table 1. Continued

Study, Year of Publication	Study Design	Health Status	Medication	Quality Score (0–12)	Vascular Region	Inducing AH		Vascular EF During AH	VSMF During AH
						Method	Dose		
Ceriello et al B,[28] 2011	RCT	T2DM	6 metformin discontinued 4 wk before 5 excluded ACE inhibitors	6	Macro	OGTT	Glucose 75 g	↓ FMD	NA
Chittari et al,[29] 2011	OBS	T2DM	17 oral agents	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Kato et al A,[37] 2010	RCT	T2DM	None	9	Macro	Cookie	Carbohydrate, 75 g	↓ FMD	NA
Kato et al B,[37] 2010	RCT	T2DM	None	9	Macro	Cookie	Carbohydrate, 75 g	↓ FMD	NA
Kato et al C,[37] 2010	RCT	T2DM	None	9	Macro	Cookie	Carbohydrate, 75 g	↓ FMD	NA
Ceriello et al (1) B,[27] 2008	OBS	T2DM	None	8	Macro	IV infusion	Glucose 15, mmol/L	↓ FMD	NA
Ceriello et al (2) B,[26] 2008	RCT	T2DM	None	8	Macro	IV infusion	Glucose 15, mmol/L	↓ FMD	NA
Ceriello et al (2) C,[26] 2008	RCT	T2DM	None	8	Macro	IV infusion	Glucose 10, mmol/L	↓ FMD	NA
Ceriello et al (2) D,[26] 2008	RCT	T2DM	None	8	Macro	IV infusion	Glucose 10, mmol/L	↓ FMD	NA
Natali et al C,[45] 2008	OBS	T2DM	Unknown	11	Micro	OGTT	Glucose, 75 g	↔ ACh	↓ SNP
Stirban et al,[48] 2006	RCT	T2DM	13 insulin, 11 aspirin, 9 ACE inhibitors, 1 angiotensin receptor blocker, 6 hydroxymethylglutaryl-CoA inhibitors, 5 β-blockers, 5 diuretics, 3 calcium channel blockers	11	Macro	Test meal	Carbohydrate, 48 g	↓ FMD	NA
Kim et al,[39] 2003	OBS	T2DM	None	9	Micro	IV infusion	Glucose, 12/mg/kg per min	↓ PORH	NA
Kawano et al C,[38] 1999	OBS	T2DM	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Shige et al,[46] 1999	OBS	T2DM	None	8	Macro	Test meal	Sucrose, 75 g	↓ FMD	↔ NMD
Zhang et al B,[59] 2013	RCT	Hypertensive	None	10	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Zhang et al A,[58] 2012	RCT	Hypertensive	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Zhang et al B,[58] 2012	RCT	Hypertensive	None	11	Macro	OGTT	Glucose, 75 g	↓ FMD	NA
Ballard et al,[24] 2013	RCT	MetS	None	11	Macro	Rice milk	Mixed sugars, 23 g	↓ FMD	NA
Baynard et al B,[25] 2009	OBS	MetS	3 metformin, 2 sulfonylurea, 4 statin	11	Macro	Test meal	Carbohydrate, 80 g	↓ FMD	NA
Dye et al,[32] 2012	OBS	T1DM	Insulin monotherapy	9	Micro	IV infusion	Dextrose, 200 mg/dL	↓ PORH	NA

Some studies presented multiple health groups comparing normoglycemia and acute hyperglycemia vascular function and were therefore evaluated as individual studies (distinguished by A, B, C, or D). Authors who published multiple studies in a single year were distinguished by (1) or (2). ↓ indicates significant decrease of vascular function during acute hyperglycemia compared with normoglycemia; ↔, no significant difference in vascular function between acute hyperglycemia and normoglycemia; ↑, significant increase of vascular function during acute hyperglycemia compared with normoglycemia; ACE, angiotensin-converting enzyme; ACh, acetylcholine; AH, acute hyperglycemia; EF, endothelial function; FMD, flow-mediated dilation; IGT, impaired glucose tolerance; IV, intravenous; MetS, metabolic syndrome; NA, vascular data not available; NMD, nitroglycerin-mediated dilation; OBS, observational study; OGTT, oral glucose tolerance test; PORH, postocclusive reactive hyperemia; RCT, randomized controlled trial; SNP, sodium nitroprusside; T1DM, type 1 diabetic mellitus; T2DM, type 2 diabetic mellitus; and VSMF, vascular smooth muscle function.

Metaregression Analyses

The SMD in macrovascular endothelial function was inversely associated with age (β=−0.03; $P<0.01$), systolic blood pressure (β=−0.04; $P<0.01$), diastolic blood pressure (β=−0.05; $P<0.01$), mean arterial pressure (β=−0.05; $P<0.01$), and low-density lipoprotein cholesterol (β=−0.93; $P<0.01$; Figure 5). In turn, the SMD in macrovascular endothelial function was positively associated with the postocclusion interval of vascular assessment (β=0.36; $P=0.01$).

Table 2. Clinical Data for Each Study Included in This Meta-Analysis

Study, Year of Publication	Health Status	n (% Women)	Age, y	BMI, kg/m^2	Blood Pressure, mm Hg			Fasting Plasma Insulin, pmol/L	Fasting Plasma Glucose, mmol/L	HbA_{1c}, %	Cholesterol, mmol/L			Triglycerides, mmol/L
					SBP	DBP	MAP				Total	HDL	LDL	
Grasser et al,[34] 2014	Healthy	25 (48)	22.5±3	23.3±10	114±10	87±5	96±7	NA	NA	NA	NA	NA	NA	NA
Nakayama et al,[43] 2013	Healthy	23 (0)	44±10	23±2.1	111±8	71±6	84±7	NA	5.1±0.4	NA	NA	NA	NA	NA
Mah et al,[42] 2013	Healthy	16 (0)	21.8±3.2	24.8±NA	117±4	79±4	92±4	142.5±94.4	5.3±0.4	NA	3.7±0.8	NA	NA	3.3±5
Wang et al A,[52] 2013	Healthy	33 (64)	51.36±7.15	24.76±3.6	NA	NA	NA	NA	5.4±0.5	6±0.3	5.5±0.6	1.4±0.4	3.7±0.6	1.5±0.5
Zhang et al A,[59] 2013	Healthy	31 (48)	47.87±10.95	23.9±2.1	124±8	79±5	94±6	NA	4.8±1.1	NA	4.7±0.4	1.4±0.3	2.9±0.4	1.3±0.3
De Marchi et al,[30] 2012	Healthy	34 (50)	32.4±3.5	19±3	119±4	79±9	92±7	34.8±6.6	5.1±0.6	NA	4.3±0.7	1.5±0.2	NA	1.5±0.1
Grassi et al,[35] 2012	Healthy	12 (58)	28±2.7	23.2±4.2	NA	NA	NA	NA	4.2±0.4	NA	NA	1.5±0.4	2.5±0.4	0.7±0.3
Suzuki et al,[49] 2012	Healthy	14 (57)	33.4±11.9	20.7±2.3	106±9	64±6	78±7	NA	4.8±0.6	5.4±0.3	5±0.6	1.7±0.4	2.7±0.5	0.8±0.4
Ceriello et al A,[28] 2011	Healthy	12 (50)	50.5±8.66	28.5±10.7	117±19	78±8	91±11	73.4±15.2	4.5±1.4	4.8±0.7	4.5±2.1	1.4±0.7	2.5±1	0.9±0.7
Mah et al,[41] 2011	Healthy	16 (0)	21.6±3.2	28.7±NA	117±4	79±4	92±4	147±96	5.3±0.4	NA	3.6±0.7	NA	NA	NA
Watanabe et al,[53] 2011	Healthy	14 (43)	33.4±11.9	20.7±2.3	106±9	64±6	78±7	29.7±11.9	4.7±0.4	NA	5±0.6	1.7±0.4	2.7±0.5	0.8±0.4
Baynard et al A,[25] 2009	Healthy	10 (NA)	53±3.32	32.7±3.5	117±13	72±3	87±6	NA	4.6±0.3	5.2±0.4	5.2±1	1.3±0.3	3.2±0.95	1±0.3
Ceriello et al (1) A,[27] 2008	Healthy	22 (45)	50.5±11.73	28.5±14.5	117±26	78±10	91±15	NA	4.5±1.4	4.8±0.9	4.5±2.8	1.4±0.9	2.5±1.4	0.9±0.9
Ceriello et al (2) A,[26] 2008	Healthy	10 (40)	50.3±8.22	27.5±9.8	115±14	76±11	89±12	NA	4.5±1	4.8±0.6	4.8±1.9	1.4±1.6	2.4±1.3	0.9±1.6
Natali et al A,[45] 2008	Healthy	20 (70)	49±8.94	27.9±4	129±13	78±9	95±10	NA	5.3±NA	5.6±0.5	4.9±0.9	1.2±0.2	3.3±0.8	1.1±0.5
Weiss et al,[54] 2008	Healthy	13 (62)	48±17	24±2.2	114±14	66±7	82±10	NA	5.5±1.4	NA	NA	NA	NA	NA
Xiang et al (1) A,[57] 2008	Healthy	26 (46)	50±6	24.2±2.3	114±7	72±6	86±7	NA	4.6±0.5	NA	4.4±0.9	1.2±0.1	1.9±0.7	1.4±1.2
Xiang et al (2) A,[56] 2008	Healthy	17 (41)	39±12.37	24.1±6.6	115±20	68±12	84±15	NA	5.1±1.7	5.1±0.4	4.7±2.7	1.2±0.7	1.9±2.4	1.4±3.8
Xiang et al (2) B,[56] 2008	Healthy	15 (47)	40±11.62	23.7±7.4	111±20	24±7	53±12	NA	4.6±1.9	4.8±0.8	4.5±1.9	1.2±0.7	1.9±1.8	1.4±3
Dengel et al A,[31] 2007	Healthy	15 (53)	11.3±1.55	17.5±1.9	110±12	59±8	76±9	41.2±15.1	4.8±0.3	NA	3.8±0.8	1.2±0.3	2.3±0.6	0.8±0.4
Zhu et al,[60] 2007	Healthy	11 (0)	22.6±2.3	22.5±1.5	113±7	79±6	90±6	NA	5.2±0.2	NA	4±0.8	1.4±0.2	2.1±0.6	0.9±0.3
Arora et al A,[22] 2006	Healthy	10 (0)	27±NA	22.4±NA	122±NA	68±NA	86±NA	NA	4.8±NA	NA	4.1±NA	1.8±NA	2.2±NA	1.1±NA
Fujimoto et al,[33] 2006	Healthy	10 (0)	30±2	NA	111±12	65±8	80±9	NA	5.1±0.6	NA	4.3±0.7	1.2±0.3	NA	1.2±0.7
Tushuizen et al,[51] 2006	Healthy	17 (0)	25.4±3	23.6±1.8	116±8	75±7	89±7	33±10	4.8±0.3	5.1±0.2	4±0.6	1.4±0.2	2.2±0.6	0.8±0.3
Napoli et al,[44] 2004	Healthy	10 (40)	23±3.16	23.6±1.9	124±6	60±3	81±4	NA	5±NA	NA	NA	NA	NA	NA
Siafarikas et al,[47] 2004	Healthy	32 (66)	19.1±1.7	22.9±4.2	NA	NA	NA	NA	NA	5±0.3	4±0.8	1.3±0.4	2.2±0.7	1.2±0.7
Ihlemann et al,[36] 2003	Healthy	10 (40)	53±6.96	22.7±1.9	144±17	75±11	98±13	NA	NA	5.2±0.3	5.2±0.6	1.7±0.3	3.2±0.6	0.8±0.3
Bagg et al,[23] 2000	Healthy	10 (20)	26±6	22±2	111±10	65±8	80±9	34.2±11.4	5.2±0.3	NA	4.7±1	NA	NA	NA
Title et al,[50] 2000	Healthy	10 (40)	25.5±3.1	24±3	118±8	72±7	87±7	NA	5.3±0.7	NA	5.1±1.1	1.3±0.1	3.3±0.9	1.2±0.5
Kawano et al A,[38] 1999	Healthy	17 (35)	52.6±7.42	NA	NA	NA	NA	51.6±9.9	5±0.3	NA	4.9±0.4	1.2±0.1	3±0.4	1.5±0.2

(*Continued*)

Table 2. Continued

Study, Year of Publication	Health Status	n (% Women)	Age, y	BMI, kg/m^2	Blood Pressure, mm Hg			Fasting Plasma Insulin, pmol/L	Fasting Plasma Glucose, mmol/L	HbA_{1c}, %	Cholesterol, mmol/L			Triglycerides, mmol/L
					SBP	DBP	MAP				Total	HDL	LDL	
Williams et al,[55] 1998	Healthy	10 (30)	33±6.32	NA	NA	NA	NA	NA	3.9±1.2	3.6±0.6	4.2±0.7	1.1±0.2	2.6±0.7	1±0.4
Lavi et al,[40] 2009	Obese	56 (0)	47.9±5.8	32.1±4.3	134±13	82±6	99±8	NA	5.4±0.2	NA	5.1±0.7	1.1±0.2	3.2±0.7	1.7±0.9
Dengel et al B,[31] 2007	Obese	16 (56)	10.1±1.6	19.3±6.4	120±12	65±8	83±9	61.6±33.2	4.8±0.2	NA	4.2±0.6	1.1±0.2	2.6±0.5	1±0.6
Wang et al B,[52] 2013	IGT	33 (64)	52.88±9.2	27.8±3.1	NA	NA	NA	NA	6.1±0.5	6.5±0	5.5±1	1.2±0.3	3.1±0.8	1.8±0.9
Natali et al B,[45] 2008	IGT	16 (63)	52±20	29.5±4.8	122±12	79±8	93±9	NA	5.7±NA	5.9±1.2	5.6±1.4	1.3±0.5	3.7±1.3	1.3±0.6
Xiang et al (1) B,[57] 2008	IGT	21 (48)	51±6	24.8±3.1	110±8	72±6	85±7	NA	5.9±0.9	NA	5.2±1.1	1.2±0.2	2.3±0.7	2±1.1
Arora et al B,[22] 2006	IGT	10 (0)	65±NA	23.2±NA	134±NA	72±NA	93±NA	NA	5.3±NA	NA	4.3±NA	1.2±NA	2.1±NA	2.6±NA
Kawano et al B,[38] 1999	IGT	24 (38)	58.5±7.84	NA	NA	NA	NA	66±11.8	5.8±0.8	NA	5.3±1	1.1±0.1	3.4±0.5	1.7±0.2
Wang et al C,[52] 2013	T2DM	43 (42)	53.4±8.99	25.7±2.9	NA	NA	NA	NA	7.5±1.2	7.4±0.1	5.8±1.7	1.2±0.3	3.2±0.7	2.2±1.2
Ceriello et al B,[28] 2011	T2DM	16 (44)	51.3±10.4	29.5±13.2	123±26	80±14	95±18	107.3±15.2	7.8±8.8	8.4±1.2	5.1±3.2	1.2±0.3	2.6±0.4	1.2±1.6
Chittari et al,[29] 2011	T2DM	21 (43)	46.4±9.62	30.1±5	NA	76±8	NA	NA	7.8±1.8	7.8±1.4	4.5±0.9	1.2±0.5	2.5±0.9	1.6±0.5
Kato et al A,[37] 2010	T2DM	10 (50)	68±7.7	26.8±3.2	144±29	89±19	107±22	45±17.4	6.1±0.8	5.8±0.6	5.5±0.4	1.4±0.3	3.5±1.3	1.5±0.1
Kato et al B,[37] 2010	T2DM	10 (30)	67.6±6.2	25.8±2.5	141±26	88±23	106±24	57.6±33.6	6.1±1	6±0.3	5.2±0.7	1.5±0.3	3.7±1.8	1.3±0.2
Kato et al C,[37] 2010	T2DM	10 (30)	67.8±8.6	25.8±3.3	141±29	88±12	106±17	39.6±24.6	6.6±1	6.1±0.6	5.3±0.7	1.4±0.3	3.9±2	1.4±0.2
Ceriello et al (1) B,[27] 2008	T2DM	27 (48)	51.3±13.51	29.5±17.2	123±33	80±19	95±24	NA	7.8±11.4	7.7±1.6	5.1±4.2	1.2±0.3	2.6±0.4	1.2±1.6
Ceriello et al (2) B,[26] 2008	T2DM	10 (50)	50.3±6.96	27.5±10.1	118±17	77±12	91±14	NA	6.8±7	7.3±1	5±2.5	1.3±0.2	2±0.5	1±1.9
Ceriello et al (2) C,[26] 2008	T2DM	10 (50)	50.2±14.23	28.4±13	121±7	79±9	93±8	NA	7.7±1.3	7.9±1.6	5±2.2	1.2±0.3	2.7±0.4	1.3±0.95
Ceriello et al (2) D,[26] 2008	T2DM	10 (60)	51±17.71	28.6±11.7	122±11	80±12	94±12	NA	6±1	7.7±1.9	5.1±2.9	1.2±0.3	2.6±0.8	1.2±2.2
Natali et al C,[45] 2008	T2DM	17 (71)	58±8.25	29.3±4.1	139±17	81±8	100±11	NA	8.3±NA	7.2±2.1	4.9±1.2	1±0.3	3.29±1.1	1.5±0.4
Stirban et al,[48] 2006	T2DM	13 (NA)	56.9±10.1	30.3±3.2	136±22	79±13	98±16	NA	NA	8.5±1.8	NA	NA	NA	NA
Kim et al,[39] 2003	T2DM	8 (50)	55.9±3.7	25.4±3.2	134±7	82±6	99±7	NA	7.2±2.6	6.6±0.8	5.5±0.3	1.3±0.2	NA	2.1±0.6
Kawano et al C,[38] 1999	T2DM	17 (29)	62.2±4.95	NA	NA	NA	NA	84±22.3	7.1±0.3	NA	5.6±0.4	1.1±0.1	3.7±0.4	1.9±0.2
Shige et al,[46] 1999	T2DM	7 (29)	49.3±8	26±5	128±9	72±9	91±9	47.4±16.8	7.1±1.3	NA	4.9±13	1±0.2	NA	1.6±0.6
Zhang et al B,[59] 2013	Hypertensive	34 (50)	47.44±10.96	24.7±3.5	156±9	96±8	116±8	NA	4.7±0.6	NA	4.7±0.5	1.3±0.2	3±0.4	1.3±0.3
Zhang et al A,[58] 2012	Hypertensive	26 (50)	47.92±8.05	24.6±2.6	160±8	97±6	118±7	NA	5.3±0.5	NA	4.7±0.6	1.4±0.3	2.6±0.4	1.4±0.2
Zhang et al B,[58] 2012	Hypertensive	34 (47)	49.29±8	24.8±2.5	159±9	99±6	119±7	NA	5.2±0.6	NA	4.9±0.5	1.3±0.3	2.7±0.5	1.3±0.3
Ballard et al,[24] 2013	MetS	19 (26)	28.5±9.59	35±3.9	125±11	85±8	98±8	55±25.7	6±0.9	NA	4.7±0.9	1±0.1	2.8±0.2	1.9±0.9
Baynard et al B,[25] 2009	MetS	11 (NA)	52±3.16	34.4±5	123±7	78±3	93±4	NA	6.1±1.3	5.9±1.1	5.1±1	1±NA	3.1±0.7	2.4±1.3
Dye et al,[32] 2012	T1DM	11 (36)	14.5±3.32	21.5±9.6	105±7	61±10	76±9	NA	NA	8.3±1.2	NA	NA	NA	NA

Data are expressed as mean±SD or n. Some studies presented multiple health groups comparing normoglycemia and acute hyperglycemia vascular function and were therefore evaluated as individual studies (distinguished by A, B, C, or D). Authors who published multiple studies in a single year were distinguished by (1) or (2). BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MAP, mean arterial pressure; MetS, metabolic syndrome; NA, data not available; T1DM, type 1 diabetic mellitus; T2DM, type 2 diabetic mellitus; and SBP, systolic blood pressure.

Table 3. Effect of Acute Hyperglycemia on Vascular Function in Healthy and Cardiometabolic Populations: Quality of Evidence

Outcome Among Participants	Design (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations*	Quality of Evidence (GRADE)
Decreased EF	RCT (23)	Serious†	Not serious	Not serious	Not serious	Publication bias likely¶	Low
Decreased EF	OBS (16)	Not serious	Not serious	Not serious	Not serious	None	Low
Decreased macro-EF	RCT (19)	Serious†	Not serious	Not serious	Not serious	Publication bias likely¶	Low
Decreased macro-EF	OBS (11)	Not serious	Not serious	Not serious	Not serious	None	Low
Preserved micro-EF	RCT (4)	Very serious†	Serious§	Not serious	Very serious‖	Publication bias likely¶	Very low
Preserved micro-EF	OBS (5)	Serious‡	Not serious	Not serious	Serious‖	None	Very low
Preserved VSMF	RCT (3)	Serious†	Not serious	Not serious	Not serious	None	Moderate
Preserved VSMF	OBS (3)	Not serious	Not serious	Not serious	Not serious	None	Low

EF indicates endothelial function; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OBS, observational study; RCT, randomized controlled trial; and VSMF, vascular smooth muscle function.

*Large magnitude of effect, dose–response, plausible biases decreasing the magnitude of effect, publication bias.

†Method for allocation of concealment and participant/assessor blinding is unclear or not performed. Incomplete outcome data and selective reporting when assessing endothelial, macrovascular endothelial, microvascular endothelial, and vascular smooth muscle function during acute hyperglycemia.

‡No control population included, failure to adequately control for confounding, and incomplete follow-up when assessing microvascular endothelial function.

§Large I^2 and point estimates vary widely across studies assessing microvascular endothelial function suggesting benefit, harm, and no effect of acute hyperglycemia.

‖The 95% confidence interval of the pooled risk ratio includes both positive and negative effects of acute hyperglycemia.

¶Publication bias is strongly suspected because of the presence of asymmetry in funnel plots for randomized control trials assessing endothelial, macrovascular endothelial, and microvascular endothelial function during hyperglycemia.

Discussion

To our knowledge, this is the first systematic review and meta-analysis to assess the effect of acute hyperglycemia on vascular function. Data from 39 studies assessing endothelial function alone or in combination with VSM function during acute hyperglycemia in healthy and cardiometabolic diseased individuals were pooled and analyzed. The meta-analysis provided evidence that the average effect of acute hyperglycemia on endothelial function is decreased function, whereas VSM function was preserved in healthy and diseased individuals. Because of evidence of heterogeneity, the interpretation of the pooled effects of hyperglycemia on endothelial function should be made cautiously. Considerable heterogeneity was identified for most subgroups suggesting that the variability across studies was because of not only sampling variability but also differences in treatment effect within each study.[64] Nevertheless, the large effect sizes and 95% CIs consistently favored normoglycemia, providing evidence of treatment effect.[64] Exploration of heterogeneity with metaregression indicated that the variability across studies could be explained by differences in age, blood pressure, and low-density lipoprotein cholesterol and the postocclusion interval of vascular assessment.

Currently, there is no consensus on the effect of acute hyperglycemia on endothelial function and VSM function as studies assessing vascular function during acute hyperglycemia have presented confounding results. This meta-analysis demonstrated evidence of macrovascular endothelial dysfunction during acute hyperglycemia in healthy people, as well as cardiometabolic diseased subjects, suggesting that the pathogenesis of CVD may begin, among others, with acute hyperglycemia-mediated transient decreases in endothelial function long before the onset of morbidities, such as obesity, hypertension, or type 2 diabetes mellitus. Interestingly, the inverse

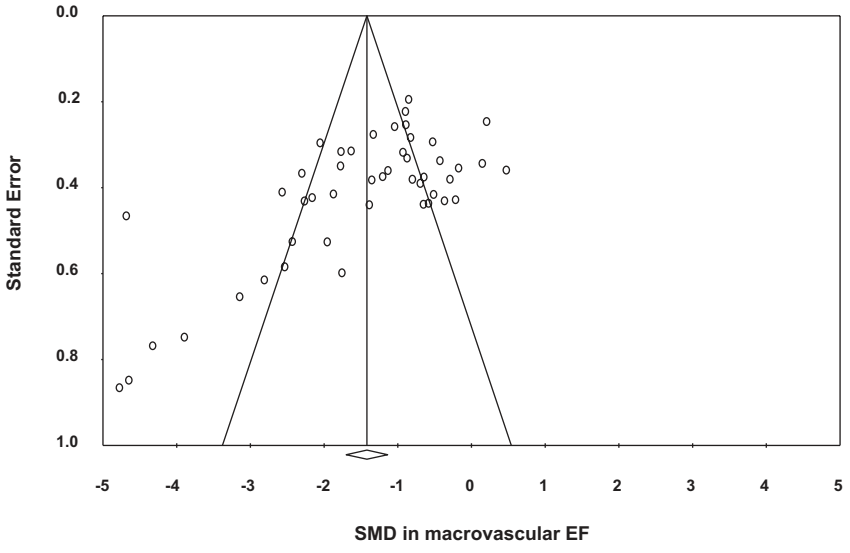

Figure 2. Funnel plot of the standardized mean difference (SMD) in macrovascular endothelial function in studies included in the meta-analysis. Funnel plot asymmetry: P=0.0002 and P=0.00005 according to Begg and Mazumdar rank correlation test and Egger test, respectively. EF indicates endothelial function.

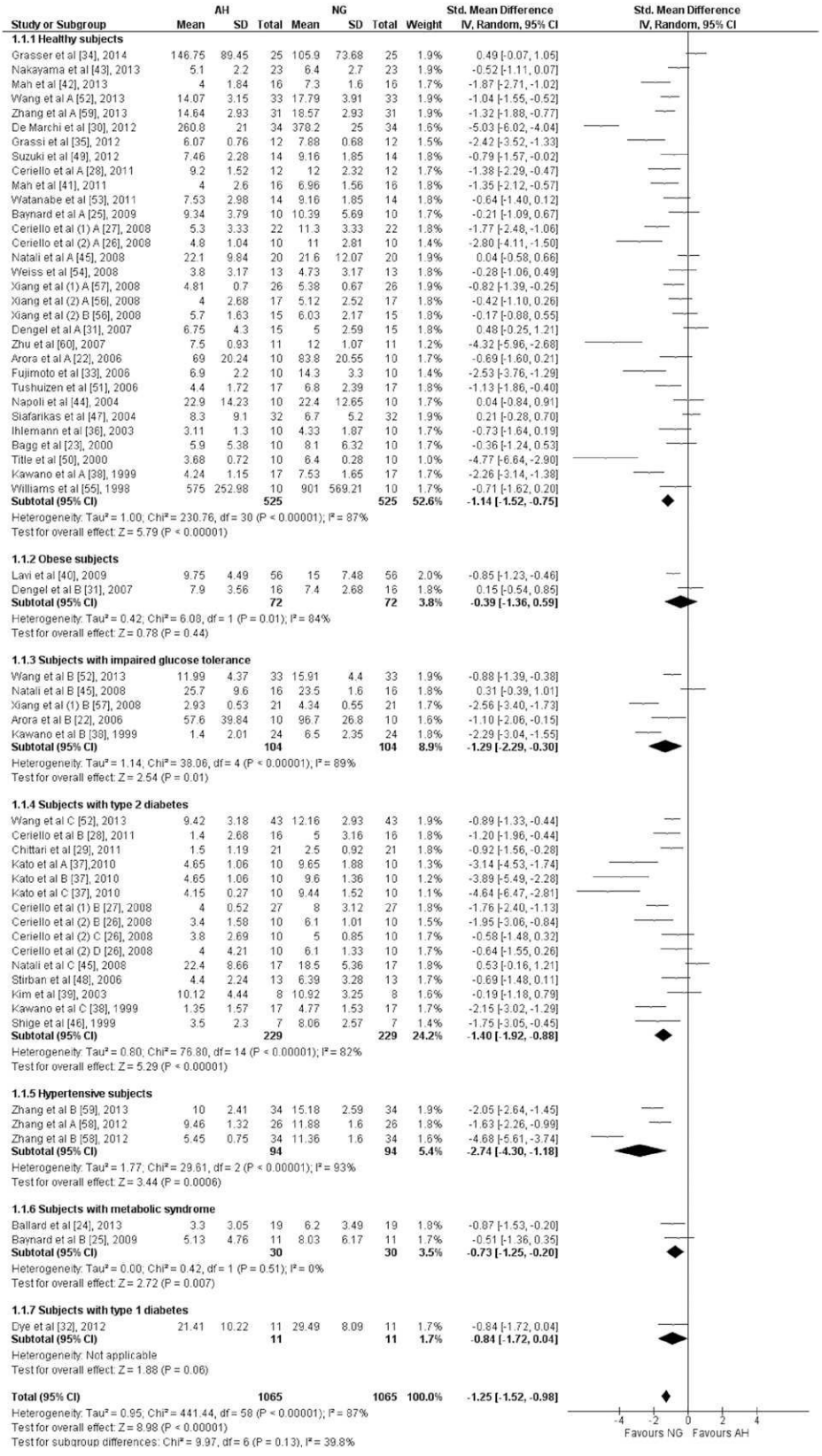

Figure 3. Forest plot of standardized mean difference (SMD) in endothelial function between acute hyperglycemic and normoglycemic states for all health groups included. Squares represent the SMD in endothelial function of each study. The diamond represents the pooled SMD in endothelial function by health group and overall. Some studies presented multiple subgroups according to health status; thus, they were evaluated as individual studies (distinguished by A, B, C, or D). Authors who published multiple studies in a single year had studies distinguished by numeric values (1 and 2). AH indicates acute hyperglycemia; CI, confidence interval; IV, inverse variance; and NG, normoglycemia.

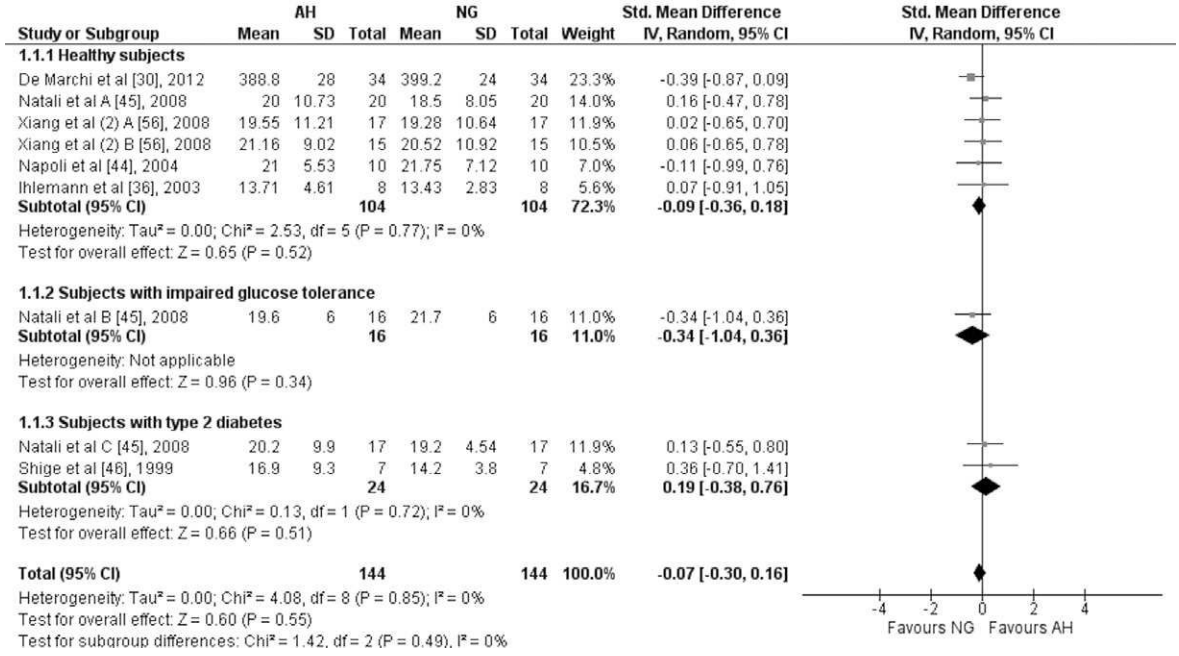

Figure 4. Forest plot of standardized mean difference (SMD) in vascular smooth muscle (VSM) function between acute hyperglycemic and normoglycemic states for all health groups included. Squares represent the SMD in VSM function of each study. The diamond represents the pooled SMD in VSM function by health group and overall. Some studies presented multiple subgroups according to health status; thus, they were evaluated as individual studies (distinguished by A, B, or C). Authors who published multiple studies in a single year had studies distinguished by numeric values (1 and 2). AH indicates acute hyperglycemia; CI, confidence interval; IV, inverse variance; and NG, normoglycemia.

relationship between macrovascular endothelial function and several traditional cardiovascular risk factors demonstrates the degree to which acute hyperglycemia mediates macrovascular endothelial dysfunction and correlates with increases in age, blood pressure, or low-density lipoprotein cholesterol levels. This is consistent with previous research revealing that elderly, hypertensive and subjects with dyslipidemia all exhibited significantly decreased endothelium-dependent vasodilation at rest compared with healthy populations,[65–67] indicating that any existing macrovascular endothelial dysfunction may therefore be compounded by an acute hyperglycemic stress. The fact that microvascular endothelial dysfunction during acute hyperglycemia was not detected contradicts previously published data that associates decreased microvascular function with incident type 2 diabetes mellitus and suggests a role for microvascular dysfunction in the pathogenesis of type 2 diabetes mellitus.[68] Although in this meta-analysis, macrovascular endothelial function was affected across healthy and cardiometabolic health groups, VSM function remained preserved during acute hyperglycemia when compared with normoglycemia. In contradiction to previous findings in animal and in vitro studies, which found VSM dysfunction mediated by VSM cell proliferation may occur in as little as 6 hours.[20,52]

Macrovascular endothelial dysfunction observed during acute hyperglycemia by methods assessing endothelium-dependent vasodilation primarily implicate decreased NO bioavailability as a central mechanism of endothelial dysfunction in healthy and cardiometabolic diseased populations.[69] This may be attributed to acute hyperglycemia increasing oxidative stress and its role in disrupting pathways of NO synthesis.[12] The fact that even healthy people exhibited decreased macrovascular endothelial function during acute hyperglycemia demonstrates how acutely NO bioavailability may be affected by excess sugar consumption. The magnitude of macrovascular endothelial dysfunction induced by acute hyperglycemia may be compounded when cardiovascular risk factors, such as increased age, blood pressure, or low-density lipoprotein cholesterol, are present. This may be partly due to the fact that health groups exhibiting these clinical markers demonstrate decreased NO bioavailability and therefore impaired endothelial function, even at rest.[65–67] Although NO is the predominant vasodilator in macrocirculation, it has been demonstrated to have significantly less influence in the microcirculatory system.[70] The increased influence of other chemical mediators of vasodilation, such as endothelial-derived hyperpolarizing factor and prostaglandin I_2,[71] may, however, explain why microvascular endothelial function remained preserved during acute hyperglycemia. Consideration should also be given to the spatial variability associated with the techniques used in several of the studies using skin microcirculation as a model of assessing microvascular function.[72] The large spatial variability in single-point laser Doppler flowmetry, for example, may have limited findings.[73] Despite this, final conclusions on the effect of acute hyperglycemia on microvascular function should not be made because of the limited availability of microcirculation data. Furthermore, it must be acknowledged that shear stress was not considered when performing analyses of flow-mediated dilation data in many studies. Shear stress, which is responsible for inducing the NO release that causes flow-mediated dilation, is dependent on variability of the hyperemic blood flow response in the microcirculation.[74]

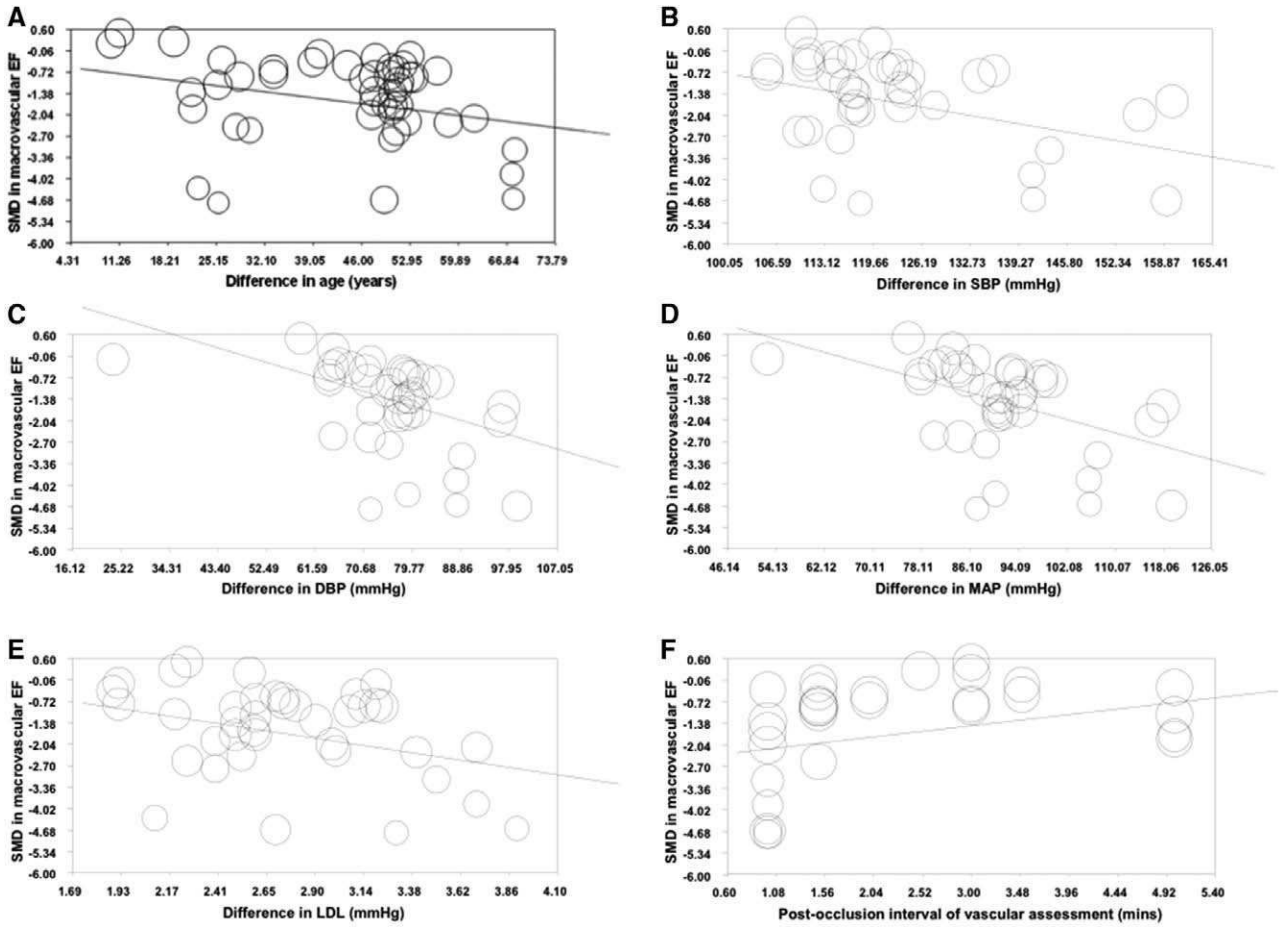

Figure 5. Metaregression plots of standardized mean difference (SMD) in macrovascular endothelial function (EF) according to the difference in (**A**) age (β=−0.03; *P*=0.005), (**B**) systolic blood pressure (SBP; β=−0.04; *P*=0.0004), (**C**) diastolic blood pressure (DBP; β=−0.05; *P*<0.00001), (**D**) mean arterial pressure (MAP; β=−0.05; *P*=0.00001), (**E**) low-density lipoprotein cholesterol (LDL; β=−0.93; *P*=0.005), and (**F**) postocclusion interval of vascular assessment (β=0.36; *P*=0.01). The size of each circle is proportional to the study's weight.

Therefore, macrovascular endothelial dysfunction observed during acute hyperglycemia may partially be mediated by a decrease in shear stress stimulus reflecting microvascular dysfunction.[74] The fact that VSM function was preserved during acute hyperglycemia indicates that endothelial dysfunction precedes VSM dysfunction, further supporting its role as a primary mechanism of CVD pathogenesis. Although disruptions in NO bioavailability mediated by acute hyperglycemia and the resulting endothelial dysfunction may initially be transient, if repeated often enough, they may lead to cumulative adverse outcomes, including proinflammatory responses and VSM cell proliferation.[12,75] It has been suggested that acute hyperglycemia may induce VSM cell proliferation by disrupting VSM cell apoptosis, which is a key mechanism to prevent increased neointimal formation and stenosis.[19] Moreover, decreased NO delivery by the endothelium to the VSM may contribute to VSM cell proliferation through increased periods of higher vasoconstrictive tone.[75] Ultimately, VSM cell proliferation may signal the beginning of a detectable and significant VSM dysfunction, representing a critical event in vascular remodeling and the development of CVD.[76]

Given that CVD is the single leading cause of death, accounting for 30% of the annual global mortality rate,[77] and that even healthy populations are subject to vascular dysfunction during acute hyperglycemia, there is a clear need to further investigate the effects of acute hyperglycemia on the underlying mechanisms of vascular function in vivo. Because of a surge in added sugar consumption in recent decades, predominantly in the form of sugar-sweetened beverages,[2] humans are more often in a state of acute hyperglycemia and therefore are more frequently inducing endothelial dysfunction. Considering this, future research should quantify what frequency and dosage of sugar consumption mediate atherosclerotic vascular changes in healthy and cardiometabolic diseased populations. Previously, certain ethnicities have demonstrated decreased vascular function at rest compared with white subjects.[78] Whether this exacerbates any vascular dysfunction mediated by acute hyperglycemia is still unknown and requires further research. To provide more comprehensive conclusions on how macrovascular and microvascular functions are affected by acute hyperglycemia, future research should consider shear stress as a covariate of conduit artery flow-mediated dilation data during statistical analyses.[79,80] Furthermore, noting that vascular function is not entirely mediated by NO,[12] future research may also investigate the effect of sugar-sweetened beverage consumption on numerous mechanisms of vasodilation (eg, NO, endothelium-derived

hyperpolarizing factor, and prostaglandin I_2) and vasoconstriction (eg, endothelin-1), the influence of which varies from microcirculation to macrocirculation.

There are many inherent limitations to our analyses that require comment. As previously discussed, significant heterogeneity was observed among studies that assessed endothelial function. Studies published in languages other than English were not included, and the quality of evidence for outcomes assessed in this meta-analysis was low-to-moderate. Subanalyses of microcirculatory and VSM data were limited because of the low number of studies assessing microvascular and VSM function in normoglycemic and acute hyperglycemic states. Furthermore, some studies used methods of assessing microcirculation that can be easily influenced by spatial variability and thus may limit results when assessing microvascular function. The risk of publication or other biases was detected when assessing the SMD in endothelial function. However, the quality of studies was evaluated by specific tools for the quality assessment of observational research,[81,82] revealing a predominantly low-bias risk. It must be acknowledged that the ethnicity of the populations was poorly reported by studies included in this meta-analysis, and thus, conclusions on the effect of ethnicity cannot be drawn from these data. Finally, many studies using flow-mediated dilation as a method of assessing macrovascular endothelial function did not report shear stress. Therefore, it was not possible to comprehensively conclude whether macrovascular endothelial dysfunction found during acute hyperglycemia is because of intrinsic abnormalities of macrovascular endothelial function or if it is partially attributable to microvascular dysfunction and decreased stimulus for conduit artery dilation.[79]

In conclusion, based on studies included in this meta-analysis, current evidence suggests that acute hyperglycemia decreases macrovascular endothelial function with no changes in microvascular endothelial function and systemic VSM function across healthy and cardiometabolic populations. This further supports endothelial dysfunction mediated by decreased NO availability as a primary mechanism in the pathogenesis of CVD, which may begin long before vascular remodeling is detectable or the onset of cardiometabolic diseases. Noting that microvascular data were limited, the microcirculatory system should therefore not be dismissed as a possible site of vascular dysfunction. Considering this, future studies should investigate the effects of sugar-sweetened beverage consumption on the underlying mechanisms of human vascular function at microvascular and macrovascular levels. These studies will provide a better understanding of how acute hyperglycemia induces vascular dysfunction and how it contributes to the pathogenesis of CVD from healthy to cardiometabolic populations.

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Disclosures

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Significance

Acute hyperglycemia has previously been proposed to contribute to vascular dysfunction, which represents one of the main precursors to CVD. However, the effect of acute hyperglycemia on mechanisms of vascular function in humans is unclear because of discrepant results. Given this, we conducted the first systematic review and meta-analysis of its kind comparing endothelial function alone or in combination with VSM function during acute hyperglycemia in healthy and cardiometabolic diseased individuals. We demonstrate that acute hyperglycemia transiently impairs macrovascular endothelial function, which may represent, among others, a primary mechanism in the pathogenesis of CVD. This is significant when considering the surge in added sugar consumption in recent decades; humans are more often in a state of acute hyperglycemia and therefore are more frequently inducing endothelial dysfunction. This study provides the foundation for future research that will investigate the effect of acute hyperglycemia on underlying mechanisms of vascular function.

Correspondence

Acute hyperglycemia impairs flow-mediated dilatation through an increase in vascular oxidative stress: winter is coming for excess sugar consumption

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In two editorials recently published in the *Journal of Thoracic Disease*, Robert P. Hoffman and John David Horowitz *et al*. separately reviewed the interaction between acute hyperglycemia and vascular function (1,2) with a focus on the results of our meta-analysis published in *Arteriosclerosis, Thrombosis and Vascular Biology* (3). We thank the authors for their interest in our research and for their contribution to further understanding the effects of acute hyperglycemia on cardiovascular health.

Hoffman importantly highlighted that although our meta-analysis defined the methods used to assess vascular function, the primary outcome of each study wasn't clearly described. Indeed, it can be confirmed that for all studies included in the meta-analysis, the percentage increase from baseline measurement in response to a specific test of vascular reactivity was the primary outcome for both microvascular data (e.g., acetylcholine and sodium nitroprusside iontophoresis) and macrovascular data (e.g., flow- and nitrate-mediated dilation); and was used to determine standardized mean difference between vascular function in the acute hyperglycemic and normoglycemic states. In agreement with Hoffman, if there is a ceiling effect to the maximal vasodilatory capability of a blood vessel, then variations in baseline measurements due to the potential vasodilating effects of increased blood glucose or blood insulin concentrations during acute hyperglycemia would limit interpretation of the results when expressing vascular data solely as the percentage increase from baseline (1). Given that only a few studies in the meta-analysis provided absolute values for baseline measurements of microcirculatory blood perfusion or brachial artery diameter, comparisons to detect differences in baseline data between the acute hyperglycemic and normoglycemic states were not possible. Such research deficiencies emphasize the need for future studies to clearly report absolute values of vascular function.

Further to this, Hoffman continued to address the potential confounding effects of the hyperinsulinemia that accompanies acute hyperglycemia. Indeed, insulin is a recognised vasodilator that contributes to vascular smooth muscle relaxation in an endothelium-dependent manner by stimulating the synthesis of nitric oxide via the PI3K/Akt pathway and the subsequent activation of endothelial nitric oxide synthase (eNOS) by phosphorylation at serine 1177 (4). Given that shear stress induces vasodilation through the same endothelium-dependent mechanism (5), it may be hypothesized that the impairment of the PI3K/Akt pathway that may be responsible for the acute hyperglycemia-mediated decrease in flow-mediated dilation may also cause a reduction in the vasodilatory action of insulin. Furthermore, it must be acknowledged that whilst blood glucose concentration increases rapidly following sugar consumption, increases in blood insulin concentration and its vasodilatory action are significantly delayed (6,7). Therefore, it is likely that the deleterious vascular effects of acute hyperglycemia may occur and be measured prior to any significant vasodilatory influence of insulin; moreover,

suggesting the redundancy of insulin's implication in potentially mediating heterogeneity between acute hyperglycemic and normoglycemic baseline measurements in vascular assessments performed soon after sugar consumption.

Considering that our meta-analysis highlighted the role of decreased nitric oxide bioavailability in acute hyperglycemia-mediated endothelial dysfunction, Horowitz *et al.* presented mechanisms that may contribute to impaired nitric oxide release (2). Nitric oxide synthesis is catalyzed by eNOS, which oxidizes L-arginine at its N-terminal oxygenase domain. However, L-arginine can also be converted to asymmetric N^G, N^G-dimethylarginine (ADMA) by protein arginine N methyltransferase (PRMT) (8) and arginase (9). The authors argue that elevated production of reactive oxygen species (ROS) during acute hyperglycemia may increase PRMT and arginase activity resulting in decreased bioavailability of L-arginine and increased ADMA. In addition to limiting substrate availability required for nitric oxide synthesis, ADMA directly competes with arginine for eNOS binding sites, thereby decreasing nitric oxide bioavailability. An increase in ROS (oxidative stress) during acute hyperglycemia may also impair eNOS activity by oxidizing its essential co-factor, tetrahydrobiopterin (BH_4) to dihydrobiopterin (BH_2) (10). Such elevations in BH_2 concentration decrease the binding of BH_4 to the active site of eNOS, compounding the superoxide generation (11) that reduces nitric oxide bioavailability and subsequently impairs endothelial function.

Given that it is now clearly established that acute hyperglycemia induces transient oxidative stress that is responsible for endothelial dysfunction (12), there is a great interest in approaches that increase antioxidant defenses that can prevent endothelial dysfunction. Physical activity is one such method that is known to stimulate antioxidant mechanisms, which may enhance eNOS coupling and eNOS activation by phosphorylation at serine 1177 (13). Nevertheless, further experimental and clinical studies are needed to explore the ability of exercise training to prevent oxidative stress and the eNOS uncoupling phenomenon occurring during acute hyperglycemia.

In conclusion, our meta-analysis provided evidence that acute hyperglycemia induces endothelial dysfunction. Due to limited availability of microcirculatory studies, this effect was contained to the macrocirculation. However, further research is needed to clearly establish that acute hyperglycemia-mediated endothelial dysfunction might also occur in the microcirculation. Given that added sugar consumption has increased dramatically in recent decades, especially in children, highlights the importance of conducting such research that will inform public health policy on the role of excess sugar consumption in the pathogenesis of cardiovascular disease.

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Footnote

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Hyperglycaemia and perivascular adipose tissue, two triggers in vascular dysfunction: Impact of oxidative stress-eNOS pathway and effect of exercise training.

The globalization of the western diet has mediated prevalence in cardiovascular disease related mortality, the single leading cause of death worldwide. Considering this, it is imperative that the underlying mechanisms of cardiovascular dysfunctions are continually investigated to establish a greater understanding of its pathogenesis from a healthy state to the presence of cardiometabolic diseases; and to improve upon current treatment and preventative strategies. Therefore, the **first aim** of this research was to identify vascular impact of acute hyperglycaemic stress induced by sweet sugar beverage consumption, with a translational approach. The results of this study demonstrated that consumption of a single commercially available sugar-sweetened beverage (SSB) induced transient micro- and macrovascular endothelial dysfunction, even in a healthy population. Further exploration into the underlying mechanisms of SSB-mediated endothelial dysfunction indicated that an increase in oxidative stress disrupts normal function of the nitric oxide pathway. Although disturbances in cardiovascular function may initially be transient, repetitive acute metabolic stress may translate to chronic cardiometabolic disease. Therefore, the **second aim** of this research was to assess the impact of a chronic metabolic disorder, metabolic syndrome (MetS), on vascular function in a rat model. Despite increasing sympathetic activity, the MetS rats didn't present elevated arterial pressure. Such findings may be explained by a compensatory adaptation of endothelial function that increases production of nitric oxide in response to α-adrenergic agonist and, thus, regulates arterial pressure despite sympathetic hyperactivity. Considering this, the **third aim** of this research evaluated the impact of perivascular adipose tissue (PVAT) on vascular fucntion in MetS rats; demonstrating that MetS altered the adiponectin-endothelial nitric oxide synthase pathway in PVAT, in an oxidative stress-dependant manner. Exercise training is well recognized as a non-pharmacological strategy that has a beneficial impact on both metabolic and cardiovascular disorders via an improvement in function of the nitric oxide pathway. Considering this, research also assessed the efficacy of this approach to prevent vascular injury induced by acute hyperglycaemia in a healthy population and by PVAT in those with MetS. It was demonstrated that exercise attenuated acute hyperglycemia-mediated endothelial dysfunction; and restored endothelium-dependent vascular reactivity in rats with MetS, due to an improvement in the biocommunication between PVAT and arterial issue and a notable enhancement of the adiponectine-endothelial nitric oxide synthase pathway.

Hyperglycémie et tissu adipeux, deux acteurs de la dysfonction vasculaire : Implication du couple stress oxydant – eNOS et modulation par l'exercice physique.

Les troubles métaboliques caractéristiques d'une alimentation de type « Western diet », sont à l'origine de pathologies cardiovasculaires, première cause de mortalité dans le monde. Il apparait nécessaire d'améliorer la compréhension des mécanismes impliqués dans l'installation des dysfonctions cardiovasculaires afin de pouvoir proposer des stratégies thérapeutiques ou préventives adaptées. Ainsi, **le premier objectif de la thèse** a été d'évaluer les effets d'une boisson sucrée sur la fonction vasculaire macro- et microcirculatoire chez des sujets sains, par une approche translationnelle allant de la clinique humaine à un modèle expérimental de rongeur. Nos résultats montrent une altération de la fonction endothéliale en réponse à une prise de boisson sucrée, dans l'ensemble des lits vasculaires. L'exploration des mécanismes sous-jacents ces altérations nous a permis d'identifier l'implication du couple stress-oxydant/voie du NO. **Un second objectif de thèse**, a été d'étudier l'impact d'un stress métabolique chronique sur la fonction vasculaire et son incidence sur la régulation de la pression artérielle. Comme observé chez certains sujets souffrant de syndrome métabolique, notre modèle de rat ne présentait pas d'hypertension artérielle, malgré une hyperactivité du système sympathique. Ceci semble être expliqué par une compensation endothéliale eNOS-dépendant, qui permet de garantir le maintien d'une pression artérielle normale en dépit de l'effet vasopresseur adrénergique élevé. Le **troisième objectif de thèse** a porté sur un nouvel élément participant au maintien de l'homéostasie vasculaire et impacté par les situations pathologiques : le tissu adipeux périvasculaire (PVAT). Nos travaux démontrent dans le contexte du SMet, une altération de la voie adiponectine/eNOS dans le PVAT, en parallèle d'une augmentation de la production d'espèces oxygénées réactives. La pratique régulière d'un exercice physique est aujourd'hui reconnue comme une stratégie non-pharmacologique permettant d'impacter à la fois les désordres métaboliques et cardiovasculaires, notamment via une amélioration de la voie du NO. Nos résultats démontrent une limitation de l'apparition des dysfonctions endothéliales causée par une hyperglycémie aigue lorsqu'un protocole d'exercice physique chronique est réalisé. Enfin, l'exercice physique permet également de prévenir les modifications des propriétés vasoactives du PVAT dans un modèle de rat SMet. Ce phénomène pourrait être expliqué par une amélioration du statut oxydant de la paroi artérielle, et à une potentialisation de la voie adiponectine/eNOS par l'exercice physique.