

do aumento do retorno venoso e, num segundo momento, da diminuição progressiva do conteúdo venoso de O_2 (CvO_2) (isto é, do aumento da extração muscular de O_2), juntamente com o incremento na oferta de O_2 circulante aos músculos ativos (Sietsema et al., 1994; Whipp et al., 2005). Portanto, a cinética da $\dot{V}O_{2p}$ na fase II depende de fatores periféricos e centrais, respectivamente. Desta forma, a cinética prolongada nos nossos pacientes com IC poderia ser resultante de limitações do DC e/ou inadequação do fluxo na microcirculação, sugerindo que o tratamento atual da IC não é capaz de corrigir essas alterações.

No contexto clínico, a questão é ainda mais complexa por causa dos potenciais efeitos do tratamento farmacológico contemporâneo da IC sobre os principais determinantes da oferta de O_2 em pacientes com IC. Mais especificamente, os antagonistas ou inibidores do sistema renina-angiotensina-aldosterona associados a β -bloqueadores têm-se mostrado eficazes em melhorar a disfunção endotelial relacionada à IC (Nakamura, 2004; Poelzl et al., 2006) e em reduzir a hiperatividade simpática nos membros (De Matos et al., 2004; Doughty, White, 2007), com efeitos positivos sobre o \dot{Q}_m esquelético (Onder et al., 2006; Poelzl et al., 2006). Logo, tais avanços no tratamento da IC poderiam ter melhorado a dinâmica da oferta muscular de O_2 de tal forma que a inércia metabólica intramuscular passaria a ser o principal fator limitante da cinética da $\dot{V}O_{2p}$. No entanto, no presente estudo, diversas variáveis medidas e estimadas sugerem que esse parece não ser o caso, ao menos durante o exercício intenso em homens não treinados com IC estável.

Dentro do aspecto funcional, há fatores que não apenas a hiperatividade simpática presente na IC contribui para a redução do \dot{Q}_m como pode ser observado no estudo de Santos et al. (2005) que observaram melhora da perfusão muscular somente quando inibiram a vasoconstrição simpática, por meio de bloqueador adrenérgico, associada a, ativador do fator relaxante do endotélio, o qual aumenta a disponibilidade de óxido nítrico. Demonstrando que na IC a hiperatividade simpática e a disfunção endotelial contribuem para redução do fluxo sanguíneo no exercício.

Estudos em diversas populações têm demonstrado que, durante o exercício, a cinética da oxigenação muscular periférica pode fornecer informações úteis sobre os efeitos de intervenções na dinâmica da oferta de O_2 em relação ao $\dot{V}O_{2m}$ (Bauer

et al., 2007; Chiappa et al., 2008, 2009). A análise da $\Delta[\text{deoxi-Hb+Mb}]$, ou seja, um índice da fração de O_2 extraída, reflete o balanço entre \dot{Q}_m e $\dot{V}\text{O}_{2m}$ (DeLorey et al., 2003; Grassi et al., 2003; Ferreira et al., 2006).

Nossos dados demonstraram que pacientes com IC apresentaram cinética da extração microvascular muscular de O_2 mais rápida (estimada pela $\Delta[\text{deoxi-Hb+Mb}]$) e cinética mais lenta da fase II do que os controles, sugerindo que a oferta microvascular de O_2 esteve comprometida nos pacientes com IC, dados também observados em estudo experimental com ratos portadores de IC (Diederich et al., 2002, Ferreira et al., 2006). Além disso, no presente estudo a razão $\tau\dot{V}\text{O}_{2p}/MRT-\Delta[\text{deoxi-Hb+Mb}]$ esteve intimamente relacionada à cinética global de ajustes cardiovasculares centrais e à tolerância ao exercício. Entendemos que os resultados são de especial importância clínica, pois os pacientes estavam com terapêutica otimizada e possíveis efeitos de confusão, como treinamento físico prévio e comorbidades (como anemia e diabetes), foram cuidadosamente evitados. É necessário, contudo, salientar que a ordem da velocidade das respostas foi semelhante em pacientes e controles, ou seja, $\Delta[\text{deoxi-Hb+Mb}]$, $\dot{V}\text{O}_{2p}$ e DC. Consequentemente é possível que a taxa insuficiente de oferta microvascular de O_2 também tenha limitado a taxa de aumento do $\dot{V}\text{O}_{2m}$ em nossos controles de meia idade, ainda que em menor extensão. O estudo de DeLorey et al. (2005) demonstrou cinética mais lenta da $\dot{V}\text{O}_{2p}$ e cinética acelerada da $\Delta[\text{deoxi-Hb+Mb}]$ em idosos saudáveis comparado a jovens saudáveis. Behnke et al. (2007) e Eklund et al. (2005) demonstraram em estudos prévios que a idade potencializa os efeitos da IC na redução na oxigenação microvascular muscular e no \dot{Q}_m , respectivamente.

No presente estudo, os pacientes com IC apresentaram uma cinética global da $\Delta[\text{deoxi-Hb+Mb}]$ mais rápida (ou seja, valores mais baixos de MRT), por causa da taxa de mudança mais rápida (τ), apesar de valores inalterados de TD . Consequentemente, parece que a fase II do fluxo sanguíneo microvascular esteve particularmente prejudicada em nossos pacientes, o que confirma os achados de Ferreira et al. (2006) no estudo realizado em ratos com IC. Após uma rápida resposta inicial, observamos um “overshoot” transitório na resposta da $\Delta[\text{deoxi-Hb+Mb}]$ na maioria dos pacientes com IC (7/10 pacientes), sugerindo que a fração de O_2 extraída aumentou acima do estado estável por causa do comprometimento

do \dot{Q}_m em relação ao $\dot{V}O_2$. Corroborando com esse conceito, os estudos com modelagens matemáticas demonstraram que a cinética do CvO_2 ($P_{mv}O_2$) relacionam-se com o \dot{Q}_m , e dependem da interação entre $\dot{V}O_{2m}$ e \dot{Q}_m (Ferreira et al., 2005a, 2005b; Bauer et al., 2007; Poole et al., 2007). Dessa forma, uma cinética prolongada do \dot{Q}_m em relação ao $\dot{V}O_{2m}$ pode resultar em atraso no incremento (TD) e “undershoot” no CvO_2 (isto é, “overshoot” na $\Delta[\text{deoxi-Hb+Mb}]$). Os estudos de Barbosa et al. (2010) e Ferreira et al. (2005a), também com modelagens matemáticas, demonstraram associação entre a área do “overshoot” e a redução do \dot{Q}_m .

A presença de “overshoot” na $\Delta[\text{deoxi-Hb+Mb}]$ (“undershoot” no sinal da $P_{mv}O_2$) tem sido demonstrada não somente em modelagens matemáticas (Ferreira et al., 2005a), mas também em estudos envolvendo seres humanos e animais em condições saudáveis e patológicas (Bauer et al., 2007; Padilla et al., 2007).

Curiosamente, esse padrão de resposta é qualitativamente semelhante ao “undershoot” das respostas de $P_{mv}O_2$, previamente observado durante o exercício no músculo de pacientes diabéticos (Padilla et al., 2007) e em animais com IC (Kindig et al., 1999; Diederich et al., 2002; Behnke et al., 2004, 2007), e idêntico ao perfil da $\Delta[\text{deoxi-Hb+Mb}]$ descrita em pacientes com diabetes tipo II (Bauer et al., 2007) e com DPOC (Chiappa et al., 2008). Esse padrão específico de resposta pode estar relacionado à redução transitória da $P_{mv}O_2$ que parece ser grande o suficiente para reduzir o gradiente de difusão do capilar para a mitocôndria, desse modo prejudicando o fluxo de O_2 e restringindo a taxa de aumento do $\dot{V}O_{2m}$ (Ferreira et al., 2005a, 2005b; Poole et al., 2007). Portanto, na tentativa de manter uma taxa adequada de incremento do $\dot{V}O_2$, ocorreria aumento na velocidade de extração tissular de O_2 , resultando assim em elevação mais pronunciada e rápida da $\Delta[\text{deoxi-Hb+Mb}]$ (ou, de forma inversa, da $P_{mv}O_2$). Sua interpretação vem sendo realizada de maneira qualitativa, como resultado de lenta oferta de O_2 em relação ao $\dot{V}O_2$. Os nossos achados indicam que há comprometimento do \dot{Q}_m em relação ao $\dot{V}O_{2m}$ nos pacientes com IC, não somente por causa da aceleração da cinética da $\Delta[\text{deoxi-Hb+Mb}]$ presente nos pacientes, mas também à presença de “overshoot”.

Nossos resultados adicionam informações a estudos anteriores que utilizaram medições baseadas em *NIRS* durante exercício incremental ou exercício de

pequena massa muscular em pacientes com IC (Wilson et al., 1989; Matsui et al., 1995). De fato, o único estudo que observou a cinética da $\Delta[\text{deoxi-Hb+Mb}]$ no início do exercício de intensidade moderada avaliou pacientes com IC após transplante cardíaco. Curiosamente, esses autores não encontraram diferenças significativas na cinética da $\Delta[\text{deoxi-Hb+Mb}]$ em transplantados versus controles normais, apesar de uma cinética da $\dot{V}O_{2p}$ mais lenta nos transplantados (Lanfranconi et al., 2006). Os resultados sugerem que as anormalidades metabólicas presentes nos músculos esqueléticos foram o principal mecanismo para a cinética mais lenta da $\dot{V}O_{2p}$ nesses pacientes, o que está em contradição com os achados em pacientes menos graves.

Reciprocamente, os dados do presente estudo são consistentes com estudos anteriores em animais, os quais sugerem que o comportamento da $P_{mv}O_2$ (e, possivelmente, $\Delta[\text{deoxi-Hb+Mb}]$ no sentido inverso), é extremamente influenciado pela gravidade da doença em ratos com IC, ou seja, uma rápida cinética da $P_{mv}O_2$ está associada a um sinal de “undershoot” na IC moderada e a uma dinâmica mais lenta da $P_{mv}O_2$ sem “undershoot” na IC mais avançada (Diederich et al., 2002; Behnke et al., 2007). Os resultados foram interpretados como evidência de que na IC grave a redução da oferta microvascular de O_2 é proporcional ao comprometimento do metabolismo oxidativo muscular, que está mais lento do que as rápidas taxas de mudança na $P_{mv}O_2$ (Diederich et al., 2002; Behnke et al., 2007). Durante oclusão arterial, Zelis et al. (1974) encontraram taxas mais lentas de desoxigenação no músculo de pacientes com IC grave. Na mesma linha, Diederich et al. (2002) e Behnke et al. (2007) encontraram taxas mais lentas de redução da $P_{mv}O_2$ em ratos com IC grave versus moderada. Dessa forma, a gravidade das alterações musculares periféricas influencia a relação oferta-utilização de O_2 e, portanto, as taxas de variação da $P_{mv}O_2$ e da $\Delta[\text{deoxi-Hb+Mb}]$.

O argumento fundamental a favor da resposta da $\Delta[\text{deoxi-Hb+Mb}]$ como índice não invasivo da dinâmica da fração de O_2 extraída são as características semelhantes entre as respostas da $\Delta[\text{deoxi-Hb+Mb}]$ em relação à mensuração da dinâmica de extração de O_2 na musculatura esquelética (Grassi et al., 2002) e às simulações realizadas em computador (Ferreira et al., 2005b). Portanto, este é o primeiro estudo a confirmar a importância da $\Delta[\text{deoxi-Hb+Mb}]$ para a mensuração da dinâmica de extração de O_2 em pacientes com IC.

Existem várias explicações para uma cinética da oferta microvascular de O_2 persistentemente anormal no início do exercício, apesar da otimização terapêutica. Em primeiro lugar, a cinética do DC foi significativamente mais lenta em pacientes com IC em relação aos controles. O potente efeito β -bloqueador cardíaco do carvedilol pôde ser relevante (Doughty, White, 2007), pois o *MRT-FC* foi ~ 80% menor nos pacientes com IC em relação aos controles. Um estudo com idosos e β -bloqueadores não seletivos encontrou uma cinética da $\dot{V}O_{2p}$ mais lenta no exercício (Hughson, Smyth, 1983) e Guazzi e Agostoni (2000) relataram que o carvedilol não melhorou a cinética da $\dot{V}O_{2p}$ em pacientes com IC moderada. Apesar dos efeitos positivos dos β -bloqueadores sobre a mortalidade da IC (Packer et al., 1996), a maioria dos grandes ensaios clínicos randomizados não conseguiu demonstrar efeito benéfico significativo de novos β -bloqueadores na tolerância ao exercício submáximo (Doughty, White, 2007). Além disso, os efeitos positivos do carvedilol relacionados ao bloqueio α -adrenérgico no tônus vascular poderia também ter desaparecido ao longo do tempo (Kubo et al., 2001). Importante ressaltar que os nossos pacientes foram terapêuticamente otimizados de acordo com as diretrizes clínicas atuais (Dickstein et al., 2008; Hunt et al., 2009), que não incluem avaliação da cinética da $\dot{V}O_{2p}$ para titular as doses das medicações. Consequentemente, não podemos descartar que seriam necessárias doses mais elevadas de IECA/BRA para compensar os efeitos potencialmente deletérios do β -bloqueio na dinâmica da oferta microvascular de O_2 na transição do exercício leve para o intenso. Em segundo lugar, apesar das possíveis melhorias no desempenho cardiovascular “central”, o tratamento farmacológico pode não ter melhorado o comprometimento da função microvascular muscular da IC (Nakamura, 2004; Poelzl et al., 2006). De fato, estudo recente, que combinou *NIRS* e espectroscopia de ressonância magnética ^{31}P , descobriu que a cinética de recuperação da [deoxi-Hb+Mb] foi mais lenta do que a da fosfocreatina após exercícios de extensão de uma única perna em pacientes com IC classe funcional da *NYHA* II e III (Kemps et al., 2010). Os achados sugerem que o comprometimento da função microvascular pode ter contribuído para limitar a disponibilidade muscular de O_2 , pois o tipo de exercício não foi associado a aumento substancial na demanda central cardiovascular. Enfim, deve-se enfatizar que os pacientes do nosso estudo foram submetidos a exercício supralimiar anaeróbico, predispondo assim uma cinética da $\dot{V}O_{2p}$ limitada pela oferta (Poole, Jones, 2005).

Contudo, esse domínio da intensidade do exercício foi considerado o mais adequado para testar a hipótese principal do estudo, pois colocaria carga maior do que a usual para o sistema cardiovascular em tratamento. De fato, apesar do teste de exercício ter sido realizado em intensidades submáximas, a $\dot{V}O_{2p}$ no *Tlim* foi muito semelhante à $\dot{V}O_{2p}$ de pico, sugerindo o desenvolvimento de um marcador do exercício de alta intensidade, ou seja, o componente “lento” da $\dot{V}O_{2p}$ (Poole, Jones, 2005).

A despeito da utilização de metodologia não rotineira na avaliação de fluxo sanguíneo periférico e de várias limitações do estudo, acreditamos que os nossos dados indicam que os pacientes com IC mesmo com tratamento otimizado apresentaram evidências de desequilíbrio no acoplamento temporal entre oferta-utilização microvascular de O_2 pela musculatura periférica na transição do exercício leve para o intenso. Portanto, os nossos dados sugerem que os distúrbios cardiocirculatórios centrais parecem ser fatores preponderantes em limitar a rapidez dos ajustes cinéticos da $\dot{V}O_{2p}$ e, provavelmente, influenciam negativamente a tolerância ao exercício intenso dessa população de pacientes.

LIMITAÇÕES DO ESTUDO

Em consequência da natureza transversal e não invasiva do presente estudo, há vários aspectos metodológicos e interpretativos a serem esclarecidos.

Algumas considerações devem ser feitas em relação ao uso da Δ [deoxi-Hb+Mb] mensurada pela *NIRS*. Assumimos que este sinal reflete a extração muscular de O_2 ($C(a-v)O_2$), assim como em outros estudos (Ferreira et al., 2005b; Bauer et al., 2007; Chiappa et al., 2008; Poole et al., 2008). O sistema utilizado (*NIRO 200[®]*) não fornece os dados da [deoxi-Hb+Mb] em valores absolutos, permitindo avaliar somente sua variação de resposta. Nós, como outros (Grassi et al., 2003; DeLorey et al., 2005; Ferreira et al., 2005a, 2005b), assumimos que a mensuração da cinética da Δ [deoxi-Hb+Mb] em um único sítio refletiu a evolução temporal da fração de O_2 muscular extraída após o início do exercício. Contudo, existe grande heterogeneidade na distribuição do \dot{Q}_m e $\dot{V}O_{2m}$ (Koga et al., 2007), que pode ser mais relevante nos músculos mal perfundidos de pacientes com IC.

Conseqüentemente é improvável que um único local de avaliação forneça descrição completa da gama de relacionamentos intramusculares individuais de oferta e utilização microvascular de O_2 . Embora existam controvérsias a respeito dos determinantes primários do sinal da *NIRS* (Tran et al., 1999; Lai et al., 2009), vários estudos têm usado $\Delta[\text{deoxi-Hb+Mb}]$ a partir de um único sítio no músculo quadríceps femoral, como aproximação da fração de O_2 tecidual extraída (DeLorey et al., 2003; Grassi et al., 2003; Ferreira et al., 2005a, 2005b), provendo extensa discussão sobre o assunto.

Adicionalmente, os sinais da Hb e Mb não são diferenciados; entretanto, como a Hb possui quatro vezes mais sítios de ligação com o oxigênio, isto não tem sido considerado crítico (Ferrari et al., 2004). Entretanto, outro ponto de preocupação é a potencial diferença entre as populações na contribuição relativa da Mb para o sinal da $\Delta[\text{deoxi-Hb+Mb}]$ (Mancini et al., 1994; Tran et al., 1999), o que poderia impactar na magnitude e na taxa de desoxigenação muscular. Lai et al. (2009), utilizando uma abordagem de biologia de sistemas, verificaram que a contribuição da Mb para todo o sinal da *NIRS* poderia ser maior durante a hipóxia comparado à normóxia. Supondo que o músculo esquelético de pacientes com IC contrai sob condições mais hipóxicas em relação aos controles saudáveis, não descartaremos a hipótese de que a contribuição da Mb para a $\Delta[\text{deoxi-Hb+Mb}]$ tenha sido maior nos pacientes. No entanto, a Mb tem valores menores de P_{50} do que a Hb, efeito que tenderia a prolongar, e não acelerar, a taxa de desoxigenação muscular nos pacientes com IC.

Outro aspecto importante é que utilizamos a cinética do componente primário da $\dot{V}O_{2p}$ como indicador da dinâmica do $\dot{V}O_{2m}$ (Barstow, Mole, 1987; Grassi et al., 1996). No entanto, deve-se reconhecer que a utilização de função monoexponencial, embora estatisticamente justificável, não é evidência de mecanismos metabólicos semelhantes nas duas populações, especialmente durante o exercício de alta intensidade. Mais especificamente, é pouco provável que a contribuição relativa da glicólise anaeróbica para a regeneração de ATP tenha sido equivalente nos pacientes e nos controles (Poole, Jones, 2005). Portanto, reconhecemos também que um \dot{Q}_m mais lento pode ter induzido uma discrepância temporal entre a cinética do $\dot{V}O_{2m}$ e a cinética da $\dot{V}O_{2p}$, em que a resposta da $\dot{V}O_{2p}$ tenha sido mais rápida

do que a dinâmica do $\dot{V}O_{2m}$, por causa das mudanças no atraso do trânsito perna-pulmão (Barstow, Mole, 1987). Assim, podemos ter subestimado a desaceleração da cinética de O_2 muscular em pacientes com IC durante exercício de alta intensidade.

Há considerações clínicas que devem ser reforçadas para evitar extrapolação generalizada dos nossos resultados. Vários pesquisadores relataram que a probabilidade de distúrbios intramusculares graves está aumentada em pacientes no estágio final da doença cardíaca (Lanfranconi et al., 2006; Jendzjowsky et al., 2007) e também em ratos com IC grave (Diederich et al., 2002; Behnke et al., 2007). Considerando que os nossos pacientes eram apenas moderadamente comprometidos, é necessário testar os resultados do presente estudo em humanos com doença mais avançada. Contudo, nossos pacientes sedentários nunca haviam sido submetidos a reabilitação cardíaca, o que os predispõem a disfunção grave no metabolismo oxidativo muscular.

Nós também admitimos que a resposta de “overshoot” na $\Delta[\text{deoxi-Hb+Mb}]$ (ou “undershoot” na $P_{mv}O_2$) é mais provável de ser encontrada em indivíduos mais velhos (Eklund et al., 2005; Behnke et al., 2007), como os avaliados neste estudo. Assim, nossos resultados devem ser vistos sob a perspectiva de que o processo de envelhecimento esteja subjacente ao comportamento da $\Delta[\text{deoxi-Hb+Mb}]$ e $\dot{V}O_{2p}$ em ambos os grupos. Portanto, novos estudos são necessários para confirmar esses achados em pacientes mais jovens com IC.

Finalmente, cuidados devem ser tomados para extrapolar nossos resultados aos pacientes com IC secundária à doença isquêmica do coração, pois a etiologia da IC pode impactar os fatores determinantes da tolerância ao exercício nessa população de pacientes (De Feo et al., 2005). Adicionalmente, estudos avaliando a função microvascular e os mecanismos de regulação autonômica poderão acrescentar informações importantes sobre a relação oferta-utilização de O_2 e elucidar de maneira ainda mais precisa os papéis de cada fator para a resposta metabólica mais lenta na transição do exercício leve para o intenso em indivíduos com IC.

6. CONCLUSÕES

Os resultados obtidos no presente estudo, cuja amostra foi composta por pacientes com IC CF da *NYHA* II e III, estáveis clinicamente com terapia farmacológica adequada e um grupo controle pareado por idade e gênero, submetidos a teste submáximo de exercício até o limite da tolerância, indicaram que, na transição exercício leve-intenso:

- 1- A taxa de incremento da $\dot{V}O_{2p}$ foi significativamente mais lenta nos pacientes com IC, comparativamente aos controles, como demonstrada pela desaceleração da resposta cinética da fase II, refletindo o prejuízo do ajuste metabólico aeróbico;
- 2- Por outro lado, houve aceleração da cinética da fração de O_2 extraída pela musculatura periférica, como estimada pelas variações da $\Delta[\text{deoxi-Hb+Mb}]$ pela *NIRS*, além de resposta mais rápida da $\Delta[\text{deoxi-Hb+Mb}]$ em relação ao $\dot{V}O_{2p}$, sugerindo assim redução da oferta microvascular de O_2 , que se correlacionou significativamente com a intolerância ao exercício;
- 3- A cinética de resposta do DC foi mais lenta, associando-se com a redução na oferta microvascular de O_2 , o que pode indicar inabilidade “central” em aumentar o fluxo sanguíneo, e conseqüentemente, a ofertar O_2 de forma apropriada à demanda metabólica.

ANEXO 1 – Carta de aprovação do Comitê de Ética em Pesquisa



Universidade Federal de São Paulo
Escola Paulista de Medicina

Comitê de Ética em Pesquisa
Hospital São Paulo

São Paulo, 24 de agosto de 2007.
CEP 0935/07

Ilmo(a). Sr(a).

Pesquisador(a) PRISCILA CRISTINA DE ABREU SPERANDIO

Co-Investigadores: Adriano Candido Barroco, Dirceu Rodrigues de Almeida (orientador)

Disciplina/Departamento: Cardiologia/Medicina da Universidade Federal de São Paulo/Hospital São Paulo

Patrocinador: Recursos Próprios.

PARECER DO COMITÊ DE ÉTICA INSTITUCIONAL

Ref: Projeto de pesquisa intitulado: “Avaliação do comportamento da relação entre oferta e utilização muscular periférica de oxigênio na transição do exercício leve para o intenso em pacientes com insuficiência cardíaca”.

CARACTERÍSTICA PRINCIPAL DO ESTUDO: Intervenção diagnóstica.

RISCOS ADICIONAIS PARA O PACIENTE: Risco mínimo, desconforto leve, envolvendo coleta de sangue.

OBJETIVOS: Investigar a relação dinâmica entre a oferta e a utilização microvascular de O₂ na transição do exercício leve (sem carga) para o intenso em pacientes não treinados com insuficiência cardíaca (IC) classe funcional II e III comparado a um grupo controle de indivíduos saudáveis.

RESUMO: Serão selecionados 15 pacientes do sexo masculino, com idade entre 20 e 70 anos, portadores de IC sintomática com tratamento contemporâneo otimizado, triados no ambulatório de Miocardiopatia da Disciplina de Cardiologia da UNIFESP e 15 controles saudáveis pareados por idade e gênero. Os indivíduos serão submetidos aos seguintes procedimentos: Avaliação clínica, teste de exercício cardiopulmonar incremental e de carga constante no Laboratório de Exercício no Setor de Função Pulmonar e Fisiologia Clínica do Exercício. Além das respostas metabólicas e ventilatórias será mensurado débito cardíaco por cardioimpedância elétrica transtorácica e oxigenação muscular pela espectroscopia por raios quasi-infravermelhos.

FUNDAMENTOS E RACIONAL: A IC é uma síndrome clínica de alta incidência e mau prognóstico, caracterizada por fadiga, dispnéia e grande limitação dos esforços físicos, com incapacidade em aumentar o débito cardíaco para a demanda metabólica. Embora esta alteração possa estar relacionada com uma resposta mais lenta do consumo de oxigênio pelo miocárdio durante o exercício, nenhum estudo prévio avaliou a relação entre a resposta central e periférica em paciente com IC em tratamento otimizado.

MATERIAL E MÉTODO: Estão descritos os procedimentos a serem realizados.

TCLE: Adequado, contemplando a resolução 196/98.

DETALHAMENTO FINANCEIRO: sem financiamento externo - R\$ 2076,00.

CRONOGRAMA: 12 meses.



Universidade Federal de São Paulo
Escola Paulista de Medicina

Comitê de Ética em Pesquisa
Hospital São Paulo

OBJETIVO ACADÊMICO: Mestrado.

ENTREGA DE RELATÓRIOS PARCIAIS AO CEP PREVISTOS PARA: 23/8/2008 e 23/8/2009.

O Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/Hospital São Paulo **ANALISOU e APROVOU** o projeto de pesquisa referenciado.

1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas.
2. Comunicar imediatamente ao Comitê qualquer evento adverso ocorrido durante o desenvolvimento do estudo.
3. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes.

Atenciosamente,

Prof. Dr. José Osmar Medina Pestana
Coordenador do Comitê de Ética em Pesquisa da
Universidade Federal de São Paulo/ Hospital São Paulo

ANEXO 2 – Termo de Consentimento Livre e Esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO Para indivíduos com Insuficiência Cardíaca

“Avaliação do comportamento da relação entre oferta e utilização muscular periférica de oxigênio na transição do exercício leve para o intenso em pacientes com insuficiência cardíaca”

O objetivo deste estudo é investigar a relação entre a oferta e a utilização de oxigênio na transição do exercício leve (sem carga) para o intenso em pacientes não treinados com insuficiência cardíaca moderada a grave comparado a um grupo controle de indivíduos saudáveis.

Este estudo terá uma duração total de 3 dias, quando iremos realizar vários exames em repouso e durante o esforço. Na **visita de triagem** o médico realizará uma avaliação clínica, para identificar se você poderá participar da pesquisa. Você fará também um teste de exercício na bicicleta usando uma máscara, que permitirá que você respire normalmente, ao mesmo tempo que se consegue medir o quanto você usa de oxigênio para realizar o exercício. A carga será escolhida de acordo com a sua falta de ar e o que você agüenta fazer no seu dia-a-dia, vai subir gradativamente até o máximo que você agüentar (em geral dura de 8 a 12 minutos). Você poderá pedir a qualquer momento para interromper o teste, quando achar que não consegue mais continuar. Você estará sendo acompanhado por um médico durante todo o teste e por dois fisioterapeutas. O seu coração estará sendo monitorizado durante todo o exame através do eletrocardiograma, assim como a sua pressão, tudo isso para sua segurança durante os exames.

Na **visita 2**, você fará 2 testes na bicicleta com intervalo de 1 hora entre eles com uma carga fixa. Após 1 hora você repetirá o teste com a mesma carga do anterior com duração máxima de 4 minutos, para avaliar a reprodução dos dados. Durante os testes na bicicleta, também será realizada a avaliação do funcionamento do seu coração (cardioimpedância transtorácica), por meio da colocação de 6 pequenas peças arredondadas com gel, em contato com a sua pele: 2 no pescoço, 2 nas costas e 2 no peito. Usaremos também um aparelho para avaliar a quantidade de oxigênio que o seu músculo utiliza durante o exercício (espectroscopia por raios quasi-infravermelhos). Colocaremos uma peça pequena na parte lateral da sua coxa e fixaremos com um adesivo transparente e uma faixa escura para que a luz não entre e prejudique o exame. Ao terminar os testes na bicicleta, você ficará em repouso na sala do exercício por mais 30 minutos para descansar. No total, todos estes exames demorarão em torno de 3 horas e serão realizados no Setor de Função Pulmonar e Fisiologia do Exercício (SEFICE), da Disciplina de Pneumologia – Universidade Federal de São Paulo.

Caso ocorra alguma intercorrência durante os testes, você ficará internado no Hospital São Paulo e sob a responsabilidade da equipe da Cardiologia. Todos os medicamentos e exames que forem necessários nesta eventualidade serão realizados.

Cabe salientar que você está sendo convidado a participar de um estudo, e que a sua participação é voluntária. Você poderá desistir a qualquer momento do estudo. Se você desistir, não modificará em nada o seu tratamento e acompanhamento no Ambulatório de Cardiologia deste hospital ou qualquer atendimento de que precisar.

O teste de exercício pode desencadear: (a) falta de ar, mas que melhora após interrompermos o teste, (b) arritmias (quando o coração bate fora do ritmo normal, ou seja, palpitação) devido ao esforço maior do que está acostumado a fazer, (c) parada cardiorrespiratória, se ocorrer uma arritmia grave e neste caso, (d) morte, o que é extremamente raro. Os demais exames não trazem riscos.

Os benefícios que poderemos obter com este estudo são: (a) maior conhecimento dos mecanismos fisiopatológicos da insuficiência cardíaca durante o exercício, uma vez que é durante o esforço que ocorrem os maiores sintomas da sua doença; (b) fornecer mais informações para os médicos que tratam outros pacientes com o mesmo problema que o seu, para aprenderem e entenderem melhor os fatores que limitam o exercício.

A qualquer hora do dia você poderá esclarecer suas dúvidas ou ser atendido através de contato com o Laboratório de Exercício da Disciplina de Pneumologia (5571-8384) ou com algum profissional responsável por esta pesquisa (Dra. Priscila Cristina de Abreu Sperandio, no celular 9541-0394) ou pessoalmente de 2ª - 6ª feira no Laboratório de Exercício da Disciplina de Pneumologia.

Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) - Rua Botucatu, n 572 - Sala 14, 1º andar (telefones: 5576-4564 / 5571-1062).

A qualquer momento você poderá desistir da participação deste estudo, sem ser prejudicado em qualquer sentido.

Os dados obtidos nas suas avaliações serão mantidos em sigilo, isto é, em segredo.

Os resultados obtidos com este estudo, tanto positivos quanto negativos, serão discutidos com você.

Você terá direito a tratamento médico e indenização pela instituição em caso de danos ocorridos por causa deste estudo.

Caso você tenha gastos adicionais por causa da sua participação neste estudo, eles serão cobertos.

Eu, _____, acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo: “Avaliação do comportamento da relação entre oferta e utilização muscular periférica de oxigênio na transição do exercício leve para o intenso em pacientes com insuficiência cardíaca”. Eu discuti com a Dra Priscila Cristina de Abreu Sperandio sobre minha decisão em participar deste estudo. Ficaram claros para mim quais são os propósitos do estudo, os exames que serão realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos constantes. Ficou claro também que a minha participação é isenta de despesas e que tenho garantia de acesso a tratamento hospitalar quando necessário. Concordo voluntariamente, em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante a realização do mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

_____ Data: ___/___/___
Assinatura do paciente / representante legal

_____ Data: ___/___/___
Assinatura da testemunha

Declaro que obtive, de forma apropriada e voluntária, o Termo de Consentimento Livre e Esclarecido deste paciente ou do seu representante legal para a participação dele.

Dra. Priscila Cristina de Abreu Sperandio – Investigador Principal

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
Para indivíduos saudáveis

“Avaliação do comportamento da relação entre oferta e utilização muscular periférica de oxigênio na transição do exercício leve para o intenso em pacientes com insuficiência cardíaca”

O objetivo deste estudo é investigar a relação entre a oferta e a utilização de oxigênio na transição do exercício leve (sem carga) para o intenso em pacientes não treinados com insuficiência cardíaca moderada a grave comparado a um grupo controle de indivíduos saudáveis.

Este estudo terá uma duração total de 3 dias, quando iremos realizar vários exames em repouso e durante o esforço. Na **visita de triagem** o médico realizará uma avaliação clínica, para identificar se você poderá participar da pesquisa. Você fará também um teste de exercício na bicicleta usando uma máscara, que permitirá que você respire normalmente, ao mesmo tempo que se consegue medir o quanto você usa de oxigênio para realizar o exercício. A carga será escolhida de acordo com a sua falta de ar e o que você agüenta fazer no seu dia-a-dia, vai subir gradativamente até o máximo que você agüentar (em geral dura de 8 a 12 minutos). Você poderá pedir a qualquer momento para interromper o teste, quando achar que não consegue mais continuar. Você estará sendo acompanhado por um médico durante todo o teste e por dois fisioterapeutas. O seu coração estará sendo monitorizado durante todo o exame através do eletrocardiograma, assim como a sua pressão, tudo isso para sua segurança durante os exames.

Na **visita 2**, você fará 2 testes na bicicleta com intervalo de 1 hora entre eles com uma carga fixa. Após 1 hora você repetirá o teste com a mesma carga do anterior com duração máxima de 4 minutos, para avaliar a reprodução dos dados. Durante os testes na bicicleta, também será realizada a avaliação do funcionamento do seu coração (cardioimpedância transtorácica), por meio da colocação de 6 pequenas peças arredondadas com gel, em contato com a sua pele: 2 no pescoço, 2 nas costas e 2 no peito. Usaremos também um aparelho para avaliar a quantidade de oxigênio que o seu músculo utiliza durante o exercício (espectroscopia por raios quasi-infravermelhos). Colocaremos uma peça pequena na parte lateral da sua coxa e fixaremos com um adesivo transparente e uma faixa escura para que a luz não entre e prejudique o exame. Ao terminar os testes na bicicleta, você ficará em repouso na sala do exercício por mais 30 minutos para descansar. No total, todos estes exames demorarão em torno de 3 horas e serão realizados no Setor de Função Pulmonar e Fisiologia do Exercício (SEFICE), da Disciplina de Pneumologia – Universidade Federal de São Paulo.

Caso ocorra alguma intercorrência durante os testes, você ficará internado no Hospital São Paulo e sob a responsabilidade da equipe da Cardiologia. Todos os medicamentos e exames que forem necessários nesta eventualidade serão realizados.

Cabe salientar que você está sendo convidado a participar de um estudo, e que a sua participação é voluntária. Você poderá desistir a qualquer momento do estudo. Se você desistir, não modificará em nada sua relação de trabalho/estudo com esta universidade ou atendimento ambulatorial/hospitalar, caso necessite.

O teste de exercício pode desencadear: (a) falta de ar, mas que melhora após interrompermos o teste, (b) arritmias (quando o coração bate fora do ritmo normal, ou seja, palpitação) devido ao esforço maior do que está acostumado a fazer, (c) parada cardiorrespiratória, se ocorrer uma arritmia grave e neste caso, (d) morte, o que é extremamente raro. Os demais exames não trazem riscos.

Os benefícios que poderemos obter com este estudo são: (a) oportunidade de avaliar sua capacidade de exercício e como está o funcionamento do seu sistema cardiovascular durante o esforço; (b) orientação da melhor faixa de treinamento para quem quiser iniciar atividade física. (c) avaliar se você tem alguma alteração cardíaca induzida pelo esforço.

A qualquer hora do dia você poderá esclarecer suas dúvidas ou ser atendido através de contato com o Laboratório de Exercício da Disciplina de Pneumologia (5571-8384) ou com algum profissional responsável por esta pesquisa (Dra. Priscila Cristina de Abreu Sperandio, no celular 9541-0394) ou pessoalmente de 2ª - 6ª feira no Laboratório de Exercício da Disciplina de Pneumologia.

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A qualquer momento você poderá desistir da participação deste estudo, sem ser prejudicado em qualquer sentido.

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Os resultados obtidos com este estudo, tanto positivos quanto negativos, serão discutidos com você.

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_____ Data: ___/___/___
Assinatura do voluntário

_____ Data: ___/___/___
Assinatura da testemunha

Declaro que obtive, de forma apropriada e voluntária, o Termo de Consentimento Livre e Esclarecido deste voluntário.

Dra. Priscila Cristina de Abreu Sperandio – Investigador Principal

ANEXO 3 – Artigo publicado no *American Journal of Physiology – Heart and Circulatory Physiology*

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Microvascular oxygen delivery-to-utilization mismatch at the onset of heavy-intensity exercise in optimally treated patients with CHF

Priscila Abreu Sperandio,^{1,2} Audrey Borghi-Silva,^{1,3} Adriano Barroco,^{1,2} Luiz Eduardo Nery,¹ Dirceu R. Almeida,² and J. Alberto Neder¹

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Sperandio PA, Borghi-Silva A, Barroco A, Nery LE, Almeida DR, Neder JA. Microvascular oxygen delivery-to-utilization mismatch at the onset of heavy-intensity exercise in optimally treated patients with CHF. *Am J Physiol Heart Circ Physiol* 297: H1720–H1728, 2009. First published September 4, 2009; doi:10.1152/ajpheart.00596.2009.— Impaired muscle blood flow at the onset of heavy-intensity exercise may transiently reduce microvascular O₂ pressure and decrease the rate of O₂ transfer from capillary to mitochondria in chronic heart failure (CHF). However, advances in the pharmacological treatment of CHF (e.g., angiotensin-converting enzyme inhibitors and third-generation β-blockers) may have improved microvascular O₂ delivery to an extent that intramyocyte metabolic inertia might become the main locus of limitation of O₂ uptake (V̇O₂) kinetics. We assessed the rate of change of pulmonary V̇O₂ (V̇O_{2p}), (estimated) fractional O₂ extraction in the vastus lateralis (~Δ[deoxy-Hb+Mb] by near-infrared spectroscopy), and cardiac output (Q̇T) during high-intensity exercise performed to the limit of tolerance (Tlim) in 10 optimally treated sedentary patients (ejection fraction = 29 ± 8%) and 11 controls. Sluggish V̇O_{2p} and Q̇T kinetics in patients were significantly related to lower Tlim values (*P* < 0.05). The dynamics of Δ[deoxy-Hb+Mb], however, were faster in patients than controls [mean response time (MRT) = 15.9 ± 2.0 s vs. 19.0 ± 2.9 s; *P* < 0.05] with a subsequent response “overshoot” being found only in patients (7/10). Moreover, τV̇O₂/MRT-[deoxy-Hb+Mb] ratio was greater in patients (4.69 ± 1.42 s vs. 2.25 ± 0.77 s; *P* < 0.05) and related to Q̇T kinetics and Tlim (*R* = 0.89 and -0.78, respectively; *P* < 0.01). We conclude that despite the advances in the pharmacological treatment of CHF, disturbances in “central” and “peripheral” circulatory adjustments still play a prominent role in limiting V̇O_{2p} kinetics and tolerance to heavy-intensity exercise in nontrained patients.

blood flow; chronic heart failure; hemodynamics; near-infrared spectroscopy; oxygen consumption

THE TIME COURSE IN WHICH pulmonary oxygen uptake (V̇O_{2p}) adapts to dynamic exercise is characteristically slowed in patients with chronic heart failure (CHF) compared with age-matched controls (7, 58, 61). The slowed V̇O_{2p} kinetics (i.e., larger O₂ deficit) lead to greater reliance on O₂-independent pathways for ATP regeneration and accumulation of by-products related to increased muscle fatigability (e.g., inorganic phosphate and H⁺) (2, 56). In fact, faster V̇O_{2p} kinetics after selected therapeutic and rehabilitative strategies have been

associated with improved exercise tolerance in CHF patients (12, 48, 63), suggesting that amelioration or resolution of the impaired oxidative metabolism at the onset of exercise has important clinical implications (as reviewed in Ref. 1).

It is widely recognized that disturbances in the diffusive and/or convective transport of O₂ to skeletal muscle mitochondria (31, 41) and/or intramyocyte metabolic machinery (9, 25, 26) could explain the slowness of V̇O_{2p} kinetics in patients with cardiopulmonary and metabolic disorders (7, 51, 61). In this context, it can be anticipated that if the increase in muscle microvascular O₂ delivery (Q̇O_{2mv}) slows to a greater extent than the rate of change in muscle V̇O₂ (as estimated by the kinetics of the “primary” component of V̇O_{2p}) (2, 25, 56), fractional O₂ extraction [~changes (Δ) in the deoxygenated hemoglobin + myoglobin ([deoxy-Hb+Mb]) signal by near-infrared (NIR) spectroscopy (NIRS)] would be accelerated in CHF patients (14, 22, 23, 28). Conversely, if the rate of increase in fractional O₂ extraction is slowed in CHF patients at the onset of exercise, this would argue against a predominant role of insufficient Q̇O_{2mv} in limiting V̇O₂ kinetics, thereby suggesting that V̇O₂ dynamics are limited by a slow activation of intracellular metabolic pathways (9, 25, 26).

The dynamic relationship between Q̇O_{2mv} and O₂ utilization, however, has been to date explored only in animal models with nontreated CHF induced by myocardial infarction (5, 6, 18, 20, 35, 45). By using phosphorescence quenching to obtain intravital measurements of microvascular PO₂ (PO_{2mv}) (59), previous investigators reported that CHF was indeed associated with Q̇O_{2mv}-to-V̇O₂ mismatching, a finding that was modulated by disease severity (18, 20), fiber typing (5, 45), and senescence (6, 20). However, it is unknown whether these seminal observations are actually applicable to humans with naturally occurring CHF receiving contemporary pharmacological treatment. In fact, the last decades brought about major changes in the treatment paradigms of CHF [e.g., angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs) and β-adrenergic blockers] (17, 32), which might be effective in improving CHF-related endothelial dysfunction (49, 55) and excessive sympathetic and neurohumoral activation (16, 19) with positive consequences on muscle blood flow (52, 55). In fact, combined therapy with ACEIs and ARBs and carvedilol, a β-adrenergic antagonist with vasodilatory properties (α₁-antagonism), is particularly emphasized in clinical guidelines (17, 32). These recommendations were based on the evidence that these drugs might work synergistically to improve left ventricular (LV) ejection fraction and lessen LV remodeling with positive consequences on hospitalizations and

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survival (17, 32, 53). However, the effects of CHF on the dynamics of (estimated) muscle $\dot{Q}O_{2mv}$ -to- $\dot{V}O_2$ matching at the onset of exercise in optimally treated humans with naturally occurring forms of the disease remain unknown.

The objective of the present study, therefore, was to investigate the relationship between the dynamics of $\dot{Q}O_{2mv}$ and $\dot{V}O_2$ utilization at the onset of heavy-intensity exercise in nontrained patients with advanced CHF receiving contemporary pharmacological therapy. We tested the hypothesis that the therapeutic advances in the treatment of CHF (17, 32) might have improved $\dot{Q}O_{2mv}$ to an extent that the slowness of intramyocyte metabolic machinery would become the limiting step of $\dot{V}O_{2p}$ kinetics. For this purpose, we simultaneously assessed the rate of change of $\dot{V}O_{2p}$, $\Delta[\text{deoxy-Hb} + \text{Mb}]$, and cardiac output (QT) during an exercise bout performed above the gas-exchange threshold (GET) to the limit of tolerance (Tlim) in a group of CHF patients and age-matched controls. We reasoned that knowledge of the precise etiological mechanisms leading to the microcirculatory O_2 exchange impairment in CHF is crucial to understanding the mechanisms of exercise intolerance and the planning of effective rehabilitative strategies aimed to decrease its clinical burden in this patient population.

METHODS

Subjects

This was a prospective study involving 10 nonsmoking men recruited from the CHF Outpatients Clinic of our institution and 11 age- and sex-matched controls. Patients had an established diagnosis of CHF for at least 4 yr, three-dimensional echodopplercardiography showing left ventricle ejection fraction (LVEF) < 35%, and New York Heart Association classification scores II–III. The patients have been optimally treated for CHF for at least 3 yr (Table 1) according to the American Heart Association/American College of Cardiology treatment recommendations for stage “C” patients, i.e., reduced LVEF and current or previous symptoms of heart failure (32). No patients had a history of hospitalization or disease exacerbation in this time-frame. Patients were excluded from study if they had clinical and/or functional evidences of obstructive pulmonary disease (forced expiratory volume in 1 s-to-forced vital capacity ratio (< 0.7) anemia ($[\text{Hb}] < 13 \text{ g\%}$), exercise-induced asthma, diabetes mellitus or other metabolic diseases, unstable angina or significant cardiac arrhythmias, and myocardial infarction within the previous 12 mo. To avoid the confounding effects of physical activity on the determinants of $\dot{V}O_{2p}$ kinetics (56), no patient had ever been submitted to cardiovascular rehabilitation. The control group was also carefully selected to recruit subjects who had not take part into any exercise training program in the preceding 5 yr and had no regular physical activity either at work or during leisure time. Subjects were required to be free of chronic pulmonary, cardiovascular, immune, and metabolic diseases. Prior to entering the study all healthy controls were submitted to clinical evaluation and they were screened by pulmonary function tests, analysis of blood biochemistry, electrocardiography, echocardiography, and a stress exercise testing. Study participants gave written, informed consent, and the study protocol was approved by the Institutional Medical Ethics Committee.

Study Protocol

After familiarization, subjects performed a ramp-incremental exercise test (5–10 W/min in patients and 15–20 W/min in controls) to determine parameters of aerobic function during exercise. The difference between $\dot{V}O_{2p}$ at the GET and $\dot{V}O_{2p}$ at peak exercise ($\Delta\dot{V}O_{2p\text{peak-GET}}$) was determined. On a different day, subjects were submitted to a constant-work-rate exercise test to the Tlim (s) at a $\dot{V}O_{2p}$ equivalent to

Table 1. Resting and exercise data from healthy subjects and optimally treated patients with CHF

	Controls, n = 11	CHF, n = 10
Anthropometrics/demographics		
Age, yr	62.4 ± 5.9	60.9 ± 8.8
Body mass, kg	78.4 ± 15.9	76.9 ± 13.7
Body mass index, kg/m ²	23.9 ± 3.8	22.5 ± 4.1
Echocardiography		
Left ventricle ejection fraction, %	59.7 ± 5.0	29.1 ± 8.2*
Drugs		
Diuretics		7
Spirinolactone		4
Digitalis		5
Carvedilol		10
ACE inhibitors/AR blockers		10
Incremental exercise		
Power, W	132 ± 19	83 ± 14*
$\dot{V}O_{2p}$, ml/min	1,708 ± 204	1,315 ± 192*
$\dot{V}O_{2p}$, ml · min ⁻¹ · kg ⁻¹	23.1 ± 4.2	15.1 ± 2.8*
$\dot{V}O_{2p}$, % pred	88.9 ± 10.1	53.1 ± 19.4*
$\dot{V}O_{2p\text{GET}}$, ml/min	1,080 ± 175	785 ± 128*
HR, bpm	153 ± 12	134 ± 10*
HR, % pred	95.3 ± 4.7	74.1 ± 10.9*
Constant work rate exercise		
Power, W	90 ± 13	58 ± 12*
Time to exercise intolerance, s	495 ± 168*	315 ± 103
$\dot{V}O_{2p}$, ml/min	1,684 ± 181	1,292 ± 200*
HR, bpm	145 ± 10	130 ± 9*
SV, ml	104.3 ± 16.1	80.2 ± 14.3*
QT, l/min	14.8 ± 2.1	9.9 ± 2.4*

Values are means ± SD. CHF, chronic heart failure; ACE, angiotensin-converting enzyme; AR, angiotensin-receptor; $\dot{V}O_{2p}$, pulmonary oxygen uptake; GET, gas-exchange threshold; HR, heart rate; SV, stroke volume; QT, cardiac output. * $P < 0.05$ (nonpaired *t*-test).

40–50% of the $\Delta\dot{V}O_{2p\text{peak-GET}}$ [~70–80% peak work rate]. Tlim was defined as the time point at which subjects signaled to stop exercising or could not maintain the required pedaling rate for 10 s despite being encouraged by the investigators. Subjects avoided caffeine, alcohol, or heavy meals before testing.

Measurements

Exercise tests. The tests were performed on an electronically braked cycle ergometer (Corival 400, Lode, The Netherlands) at 60 rpm and they were preceded by an unloaded baseline pedaling at 0 W for 2 min. $\dot{V}O_{2p}$ (ml/min), $\dot{V}CO_{2p}$ (pulmonary carbon dioxide output, ml/min), minute ventilation (\dot{V}_E , l/min), and end-tidal partial pressures (PET) for O_2 and CO_2 (mmHg) were measured breath by breath using a computer-based system (CardiO₂ System, Medical Graphics). Gas-exchange variables measured during the incremental test were averaged every 15 s. $\dot{V}O_{2p\text{peak}}$ was defined as the highest value achieved during the test and compared with Brazilian standards (50). Heart rate (HR, bpm) was determined by using the R-R interval from a 12-lead electrocardiogram. Arterial oxyhemoglobin saturation was determined by pulse oximetry (%; POX 010–340, Medaid) with its analog signal being directed to the system. Subjects were also asked to rate their “shortness of breath” at exercise cessation using the 0–10 Borg’s category-ratio scale. The $\dot{V}O_{2p\text{GET}}$ was estimated by the gas-exchange method, inspecting visually the inflection point of $\dot{V}CO_{2p}$ with regard to $\dot{V}O_{2p}$ (modified V-slope) and secondarily confirmed by the ventilatory method when $\dot{V}_E/\dot{V}O_{2p}$ and PET O_2 increased while $\dot{V}_E/\dot{V}CO_{2p}$ and PET CO_2 remained stable. The reading was performed independently by two experienced observers without knowledge of other results or subject identities.

Skeletal muscle oxygenation. Skeletal muscle oxygenation profiles of the left vastus lateralis were evaluated with a commercially available NIRS system (Hamamatsu NIRO 200, Hamamatsu Photonics).

The theory of NIRS has been described in detail elsewhere (21). Briefly, one fiber optic bundle carried the NIR light produced by the laser diodes to the tissue of interest while a second fiber optic bundle returned the transmitted light from the tissue to a photon detector in the spectrometer. The intensity of incident and transmitted light were recorded continuously and, along with the relevant specific extinction coefficients, used to measure changes in the oxygenation status of Hb and Mb. A set of optodes was placed on the belly of the vastus lateralis muscle midway between the lateral epicondyle and greater trochanter of the femur. The optodes were housed in an optically dense plastic holder, thus ensuring that the position of the optodes, relative to each other, was fixed and invariant. The optode assembly was secured on the skin surface with tape and then covered with an optically dense, black vinyl sheet, thus minimizing the intrusion of extraneous light and loss of NIR light.

The variables assessed by NIRS are the concentration (denoted by square brackets) of oxygenated, deoxygenated, and total Hb. Among the NIRS variables, several laboratories have adopted the [deoxy-Hb+Mb] signal as the preferred indicator of changes in muscle microvascular oxygenation during exercise (11, 14, 23, 28). The [deoxy-Hb+Mb] response to exercise is then considered a proxy of fractional O₂ extraction in the microcirculation, reflecting the balance between O₂ delivery and utilization. The device used herein did not measure the reduced-scattering of the tissue (36), preventing determination of absolute values of [deoxy-Hb+Mb] (in μM). Therefore, values were recorded as a delta (Δ) from baseline in units of micromolar per centimeter and expressed relative (%) to the amplitude of variation from baseline to the steady state.

Central hemodynamics. Q_T (l/min) and stroke volume (SV, liters) were measured noninvasively throughout the constant work rate test by impedance cardiography (PhysioFlow PF-05, Manatec Biomedical). The PhysioFlow device and its methodology have been thoroughly described elsewhere (10). This methodology is different from previously used impedance systems as its algorithm does not require basal thoracic impedance measurement (Z₀). Before each exercise test, the system was autocalibrated taking into consideration age, stature, body mass, and blood pressure values. Signal quality was verified by visualizing the electrocardiography (ECG) tracing and its first derivative (dECG/dt) and the impedance waveform (ΔZ) with its first derivative (dZ/dt). In preliminary experiments the coefficient of variation for changes in Q_T and SV during exercise were 3.3 and 4.1%, respectively. In these preliminary trials the changes in Q_T measured by impedance cardiography were consistent with those predicted from V̇O_{2p} values using the submaximal Q_T-V̇O_{2p} relationship described in CHF patients (8).

Kinetics analysis. The breath-by-breath V̇O_{2p}, Δ[deoxy-Hb+Mb] and hemodynamic (Q_T, SV, and HR) data were time aligned to the start of exercise and interpolated second by second. The kinetics of these responses were determined by nonlinear regression using a least square technique (Marquardt-Levenberg, SigmaPlot 10.0, Systat Software). The V̇O_{2p} responses to exercise in the intensity domain used in our investigation are characterized by the presence of a slow component (2, 56). We checked the absence of the onset or emergence of the slow component in the first 180 s after the start of exercise by certifying that the monoexponential fit (Eq. 1) did not demonstrate a discernible departure from the measured response profile, i.e., maintenance of the flat profile of the residual plot. If the slow component was not discernible, we opted to fit V̇O_{2p} from 30 s of baseline pedaling to the steady-state value; otherwise, data were fitted from 30 s of baseline pedaling to 180 s after the onset of exercise. For Δ[deoxy-Hb+Mb] kinetics the analyses were conducted on data from 30 s of baseline cycling to the steady-state response to minimize distortion of the curve-fitting seen when longer periods are analyzed. Theoretical (22) and empirical studies (11, 14, 23, 28) suggest that the primary phase of the Δ[deoxy-Hb+Mb] response is complete within this time window.

The model used for fitting the kinetic response of V̇O_{2p} and Δ[deoxy-Hb+Mb] was

$$[Y]_{(t)} = [Y]_{(b)} + A \cdot (1 - e^{-(t-TD)/\tau}) \quad (1)$$

where *b* refers to baseline unloaded cycling and *A*, *TD*, and *τ* are the amplitude, time delay, and time constant of the exponential response, respectively. For V̇O_{2p} analysis we deleted the data relative to the cardiodynamic phase, which duration was individually determined according to standard procedures (2). Therefore, τV̇O_{2p} represents the time course of the primary component – an estimate of the muscle V̇O₂ kinetics (25) (see *Methodological Considerations and Interpretative Issues*). The overall kinetics of Δ[deoxy-Hb+Mb] (~time to reach 63% of the response following the onset of exercise) were determined by the mean response time (MRT = τ + TD). To relate the kinetics of O₂ utilization to the dynamics of (estimated) fractional O₂ extraction, we calculated the ratio τV̇O_{2p}/MRT-Δ[deoxy-Hb+Mb]. Therefore, the higher this ratio, the faster the Δ[deoxy-Hb+Mb] kinetics in relation to V̇O_{2p} dynamics, suggesting slower adaptation of Q̇O_{2mv} (11). For the hemodynamic data, we opted to calculate the individual half-time (*t*_{1/2}, s) as the low signal-to-noise ratio for SV and Q_T precluded an adequate monoexponential fitting in some patients. This parameter was defined as the time in which the physiological response reached half of the difference between 180 s and the onset of exercise (SigmaPlot 10.0). An estimate of MRT was then obtained as *t*_{1/2} × 1.44.

Based on previous findings with other disease populations (3, 11), we systematically looked at the presence or not of an “overshoot” in Δ[deoxy-Hb+Mb] after the initial “fast” response (see RESULTS). A two-component, monoexponential model was applied to these data:

$$[Y]_{(t)} = [Y]_{(b)} + A_1 \cdot (1 - e^{-(t-TD_1)/\tau_1}) - A_2 \cdot (1 - e^{-(t-TD_2)/\tau_2}) \quad (2)$$

where the subscripts 1 and 2 correspond to the two sequential components (upward and downward, respectively). This model was applied to adequately define the duration of the upward component, i.e., TD₂. Considering, however, the uncertainties about the actual physiological meaning of the downward component, only the describing parameters of the upward component were considered for statistical analysis. Assuming that a larger area under the Δ[deoxy-Hb+Mb] overshoot would be conceptually similar to a greater “undershoot” in the Po_{2mv} (22, 23, 57), the former variable was used as an additional index of impaired microvascular O₂ delivery. On preliminary trials, the coefficient of variation for the kinetic parameters of the Δ[deoxy-Hb+Mb] response ranged between 5–11% [1st test – 2nd test mean bias and range: τ = 0.3 s (–0.3 s to 0.8 s) and TD = 0.1 s (–0.4 to 0.5 s)].

Statistical Analysis

Results were summarized as means ± SD. To contrast between-subject resting and exercise responses, nonpaired *t* or Mann-Whitney tests were used as appropriate. Pearson’s product moment correlation was used to assess the level of association between continuous variables. The level of statistical significance was set at *P* < 0.05 for all tests.

RESULTS

Subject Characteristics and Maximal Exercise Capacity

There were no significant differences on anthropometric attributes in CHF patients vs. age-matched controls (Table 1). Etiology of CHF was mostly nonischemic and patients had severe LV dysfunction at rest. In contrast, peak work rate and peak V̇O_{2p} were only moderately reduced with eight patients being classified as Weber’s class II and two patients as class III. The GET was identified in all subjects, and patients had lower V̇O_{2pGET} than controls (*P* < 0.05). Patients showed

impaired chronotropic responses and lower tolerance to constant work-rate exercise (T_{lim}) compared with controls (Table 1; $P < 0.01$).

Pulmonary Gas Exchange and Cardiovascular Dynamics

The kinetics of $\dot{V}O_{2p}$ and hemodynamic responses were slower in patients than controls (Fig. 1 for $\dot{V}O_{2p}$ and $\dot{Q}T$; Table 2). In a subgroup of subjects in whom the tests were repeated (6 patients and 6 controls), the coefficient of variation for $\tau\dot{V}O_{2p}$ and $t_{1/2} \dot{Q}T$ averaged 8.4 and 9.9%, respectively. Estimated MRT- $\dot{Q}T$ was consistently slower than $\tau\dot{V}O_{2p}$ in both groups ($P < 0.05$) (Fig. 1; Table 1). MRT-HR was particularly impaired in patients compared with controls (CHF-controls/controls $\times 100 = 84.7 \pm 32.3\%$ and $34.7 \pm 19.5\%$ for HR and SV responses, respectively). There was a significant relationship between $\tau\dot{V}O_{2p}$ and $t_{1/2} \dot{Q}T$ only in patients ($R = 0.79$); in addition, both variables were related to T_{lim} in CHF patients ($R = -0.81$ and $R = -0.69$, respectively; $P < 0.05$) but not in controls.

Muscle Oxygenation and Estimated $\dot{Q}O_{2mv}$

The $\Delta[\text{deoxy-Hb+Mb}]$ response displayed a region in which the signal remained stable or decreased transiently with similar duration in both groups (time delay). After this phase, $\Delta[\text{deoxy-Hb+Mb}]$ increased rapidly with a response kinetics that were much faster than the $\dot{V}O_{2p}$ and $\dot{Q}T$ responses in both groups (Figs. 1 and 2; Table 2).

There were substantial differences in the $\Delta[\text{deoxy-Hb+Mb}]$ dynamics in patients vs. controls. Therefore, $\tau\Delta[\text{deoxy-Hb+Mb}]$ (Figs. 1 and 2; Table 2) and MRT- $\Delta[\text{deoxy-Hb+Mb}]$ (Fig. 2) were significantly faster in patients compared with controls ($P < 0.05$). In addition, $\tau\dot{V}O_{2p}/\text{MRT-}\Delta[\text{deoxy-Hb+Mb}]$ was greater in patients (4.69 ± 1.42 s vs. 2.25 ± 0.77 s; $P < 0.05$) and an overshoot in the $\Delta[\text{deoxy-Hb+Mb}]$

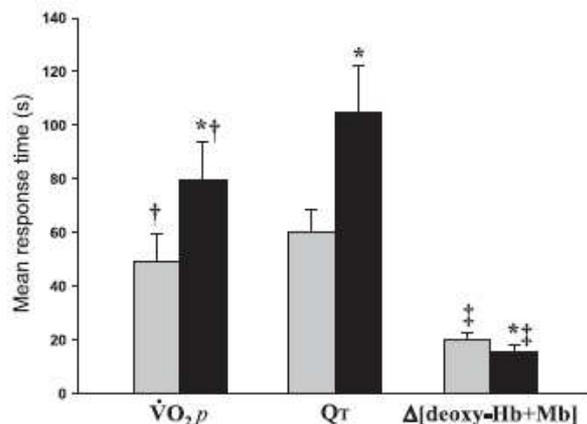


Fig. 1. Mean response time of pulmonary $\dot{V}O_2$ ($\dot{V}O_{2p}$), cardiac output ($\dot{Q}T$), and changes in deoxy-hemoglobin+myoglobin measured by near-infrared spectroscopy ($\Delta[\text{deoxy-Hb+Mb}]$; ~fractional O_2 extraction) at the onset of heavy-intensity exercise in age-matched sedentary controls (shaded bars) and optimally treated patients with chronic heart failure (CHF) (solid bars). Note that the kinetics of $\dot{V}O_{2p}$ and $\dot{Q}T$ were slower in CHF patients; in contrast, patients presented with faster $\Delta[\text{deoxy-Hb+Mb}]$ dynamics compared with healthy controls, suggesting impaired microvascular O_2 delivery. Data are means (SD). * $P < 0.05$ for between-group comparisons; † $P < 0.05$ for within-group comparisons of $\dot{V}O_{2p}$ vs. $\dot{Q}T$. ‡ $P < 0.05$ for within-group comparisons of $\Delta[\text{deoxy-Hb+Mb}]$ vs. $\dot{V}O_{2p}$ and $\dot{Q}T$.

Table 2. Kinetic parameters for $\dot{V}O_{2p}$, $\Delta[\text{deoxy-Hb+Mb}]$, and $\dot{Q}T$ by transthoracic impedance in healthy subjects and optimally treated patients with CHF

	Controls, n = 11	CHF, n = 10
$\dot{V}O_{2p}$		
Baseline, ml/min	484 ± 123	409 ± 108
Amplitude, ml/min	908 ± 134	584 ± 149*
τ , s	40.5 ± 11.3	65.3 ± 16.7*
TD, s	10.8 ± 8.7	9.5 ± 10.1*
$\Delta[\text{deoxy-Hb+Mb}]$		
Baseline, %	0.1 ± 2.1	-0.4 ± 1.9
Amplitude, %	96.4 ± 7.5	114.2 ± 9.3*
τ , s	9.3 ± 1.6	5.9 ± 1.7*
TD, s	10.7 ± 1.9	10.0 ± 2.0
$\dot{Q}T$		
Baseline, l/min	6.5 ± 1.9	4.9 ± 1.7*
Amplitude, l/min	5.2 ± 1.5	3.1 ± 1.3*
$t_{1/2}$, s	40.2 ± 7.5	70.7 ± 13.0*

Values are means ± SD. $\Delta[\text{deoxy-Hb+Mb}]$, changes in deoxy-hemoglobin+myoglobin by near-infrared spectroscopy; TD, time delay; τ , time constant; $t_{1/2}$, half-time. $\Delta[\text{deoxy-Hb+Mb}]$ values expressed relative to steady-state, baseline variation. * $P < 0.05$ (nonpaired *t*-test).

response was found in 7 of 10 patients but in no control (see Fig. 2 for a representative patient).

There was a significant relationship between $\tau\dot{V}O_{2p}/\text{MRT-}\Delta[\text{deoxy-Hb+Mb}]$ and the area under the overshoot in these patients ($R = 0.74$; $P < 0.05$). Importantly, $\tau\dot{V}O_{2p}/\text{MRT-}\Delta[\text{deoxy-Hb+Mb}]$ was also significantly related to both $t_{1/2} \dot{Q}T$ and T_{lim} (Fig. 3) in CHF patients.

DISCUSSION

This is the first study, to our knowledge, to investigate whether the dynamic matching of (estimated) $\dot{Q}O_{2mv}$ and $\dot{V}O_2$ at the onset of heavy-intensity exercise is impaired in optimally treated (17, 32) humans with CHF. We found that phase II

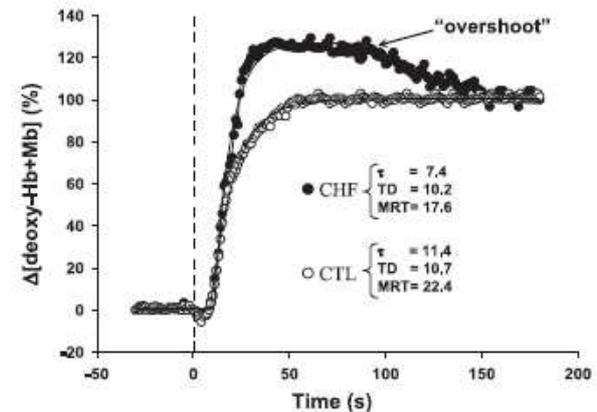


Fig. 2. $\Delta[\text{deoxy-Hb+Mb}]$ at the onset of heavy-intensity exercise in a representative age-matched control (CTL) and an optimally treated patient with CHF. Values are expressed relative to the amplitude of variation from baseline to the steady state. Note the signal "overshoot" after a more rapid rate of change in $\Delta[\text{deoxy-Hb+Mb}]$ [i.e., lower mean response time (MRT = $\tau + \text{TD}$)] in the CHF patient, suggesting a faster kinetics of fractional O_2 extraction and impaired microvascular O_2 delivery. TD, time delay; τ , time constant.

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ON-EXERCISE MUSCLE DEOXYGENATION KINETICS IN CHF

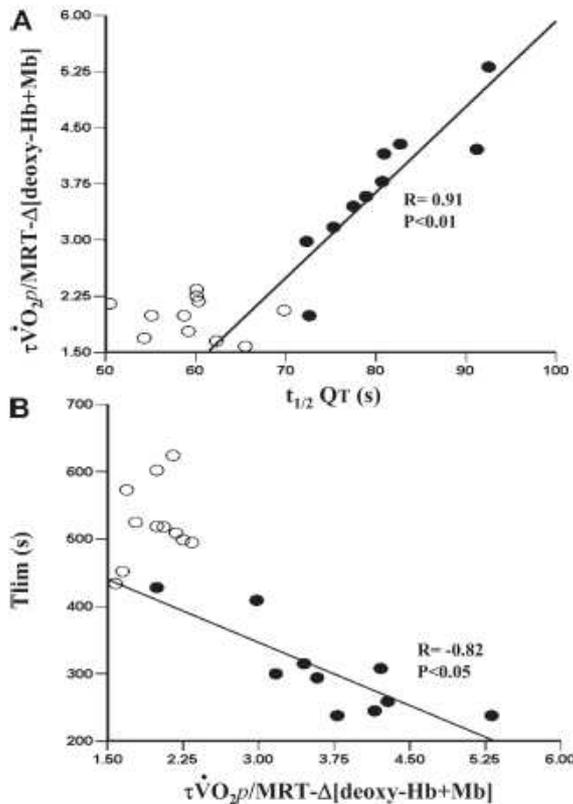


Fig. 3. Relationship between time constant of the “primary” component of the on-transient $\dot{V}O_{2p}/MRT$ of $\Delta[\text{deoxy-Hb+Mb}]$ with the dynamics of QT (A) and time to exercise intolerance (Tlim) (B) in optimally treated patients with CHF (●) and healthy controls (○). These data suggest that the sluggish kinetics of microvascular O_2 delivery have been mechanistically linked to slower “central” cardiovascular adjustments (A) and contributed to decreased exercise tolerance in CHF patients (B).

$\dot{V}O_{2p}$ kinetics were slower in patients than controls and significantly related to decreased exercise tolerance (Tlim). Patients also displayed sluggish kinetics of $\dot{Q}T$ and faster dynamics of fractional O_2 extraction ($\sim\Delta[\text{deoxy-Hb+Mb}]$ by NIRS) (11, 14, 23, 28), suggesting impaired adaptation of $\dot{Q}O_{2mv}$. This contention was further supported by the findings of higher values of the $\tau\dot{V}O_{2p}/MRT-\Delta[\text{deoxy-Hb+Mb}]$ ratio in patients, i.e., for a given rate of change in $\dot{V}O_{2p}$, $\Delta[\text{deoxy-Hb+Mb}]$ adapted more rapidly in patients than controls. Moreover, an overshoot in $\Delta[\text{deoxy-Hb+Mb}]$ signal was found in 7 of 10 patients but in none of the controls. Importantly, higher $\tau\dot{V}O_{2p}/MRT-\Delta[\text{deoxy-Hb+Mb}]$ values were associated with slower dynamics of QT and shorter Tlim (Fig. 3), suggesting that the slowness of $\dot{Q}O_{2mv}$ kinetics have been mechanistically linked to the sluggish “central” cardiovascular adjustments and contributed to decreased exercise tolerance. These data, therefore, provided evidence that contemporary pharmacological therapy (17, 32) does not preclude that central and “peripheral” circulatory disturbances still play a prominent role in limiting the initial rate of change in the muscle oxidative metabolism and tolerance to high-intensity exercise in humans with CHF.

Mechanisms for Slower $\dot{V}O_{2p}$ Kinetics in Humans With CHF

It has long been demonstrated that the dynamics of $\dot{V}O_{2p}$ are slowed in patients with CHF (7, 61) and related to a number of clinical and functional outcomes (1, 12, 48, 63). In this context, derangements of convective and diffusive O_2 delivery to mitochondria (i.e., O_2 transport) and/or impaired muscle utilization (i.e., intramyocyte metabolic inertia) may account for the prolonged $\dot{V}O_{2p}$ kinetics (56). Potential mechanisms leading to impaired O_2 delivery include the central hemodynamic effects of CHF (46, 62), heightened neurohumoral activation (16, 49), impaired nitric oxide- (24) and endothelium-dependent (4) vasodilation, and/or impaired blood flow redistribution from the nonexercising tissues to the exercising muscles (47).

Conversely, CHF is also associated with profound bioenergetic disturbances in the skeletal muscles that could also limit the rate of increase in $\dot{V}O_{2p}$ (15). For instance, $\dot{V}O_{2p}$ kinetics are not always accelerated in heart transplant recipients (39) and remain abnormal during small muscle mass exercise in which the central cardiovascular constraints are no longer operative (33). In addition, increased QT after cardiac reinnervation has not been consistently associated with faster $\dot{V}O_{2p}$ kinetics (43). Further evidence for a relevant role of intramuscular factors was provided by Zelis et al. (66), who found slower rates of NIRS-measured muscle deoxygenation during arterial occlusion in patients with severe CHF and by the findings of Diederich et al. (18) and Behnke et al. (6), who described slower, rather than faster, rates of decrease in PO_{2mv} in rat with severe vs. moderate CHF.

In the clinical context, this issue is further complicated by the potential effects of contemporary pharmacological treatment of CHF on the main determinants of O_2 delivery in patients with CHF. More specifically, ACEIs and ARBs plus β -blockers have been found to be effective in improving CHF-related endothelial dysfunction (49, 55) and reduce excessive sympathetic outflow to the limbs (16, 19) with positive effects on muscle blood flow (52, 55). Collectively, these data might indicate that such improvements in CHF treatment may have enhanced the dynamics of muscle O_2 delivery to an extent that intramuscular metabolic inertia would become the main factor limiting $\dot{V}O_{2p}$ kinetics. Several variables measured and estimated in our study suggest that this may not be the case during exercise of heavy intensity in nontrained men with stable CHF.

Microvascular O_2 Delivery During Exercise in CHF

Our data demonstrated that CHF patients showed faster kinetics of muscle microvascular fractional O_2 extraction (as estimated by $\Delta[\text{deoxy-Hb+Mb}]$) and slower kinetics of phase II than controls, suggesting that $\dot{Q}O_{2mv}$ adapted at a slower rate in patients (14, 22, 23, 28). Moreover, the ratio $\tau\dot{V}O_{2p}/MRT-\Delta[\text{deoxy-Hb+Mb}]$ was closely related to the overall kinetics of central cardiovascular adjustments and exercise tolerance (Fig. 3). These results are of particular clinical relevance because the patients have been therapeutically optimized for at least 3 yr (17, 32) and the confounding effects of training status and comorbidities (such as anemia and diabetes) have been carefully avoided. It is appropriate, however, to point out that the order of speed of responses was similar in patients and controls, i.e., $\Delta[\text{deoxy-Hb+Mb}]$, $\dot{V}O_{2p}$, and QT (Fig. 1). Consequently, it is conceivable that insufficient rates of muscle O_2

delivery also limited the rate of increase in $\dot{V}O_2$, albeit in a lesser extent, in our middle-aged to aged controls (6, 20).

NIRS is a noninvasive technique that allows continuous measurement of key determinants of peripheral muscle oxygenation during exercise (21). The time course of $\Delta[\text{deoxy-Hb+Mb}]$ in particular reflects the local balance between O_2 delivery and uptake in the area under investigation (14, 22, 23, 28). Several studies have shown that $\Delta[\text{deoxy-Hb+Mb}]$ provides a surrogate of fractional O_2 extraction (see *Methodological Considerations and Interpretative Issues*), and its measurement in parallel with (muscle) phase II $\dot{V}O_{2p}$ kinetics can give useful inferences regarding $\dot{Q}O_{2mv}$ via the Fick principle (14, 22, 23, 28). In this context, it is widely recognized that the muscle hemodynamic response at the onset of exercise is characterized by a fast "phase I" response related to the mechanical effect of muscle contraction (i.e., muscle pump) and, probably, rapid vasodilation and a slower "phase II" matched with metabolic demand, resulting from metabolic feedback control (60). In contrast, muscle $\dot{V}O_2$ response appears to be well characterized by a single monoexponential function from the start of exercise (2). Therefore, the resulting response of fractional O_2 extraction ($\sim\Delta[\text{deoxy-Hb+Mb}]$) encompass an early delay where O_2 delivery meets (or exceeds) demand (TD) and a rapidly increasing response when the dynamics of capillary flow blood is slower than the rate of change in O_2 utilization (57). In this construct, the overall $\Delta[\text{deoxy-Hb+Mb}]$ kinetics are expected to be inversely related to the dynamics of $\dot{Q}O_{2mv}$ (14, 22, 23, 28).

In the present study, CHF patients showed faster overall $\Delta[\text{deoxy-Hb+Mb}]$ kinetics (i.e., lower MRT values) due to a more rapid rates of change (τ) despite unaltered TD values. Consequently, it seems that the phase II of microvascular blood flow has been particularly impaired in our patients (22, 23). In line with this notion, we observed a transient overshoot in the $\Delta[\text{deoxy-Hb+Mb}]$ response after the initial "fast" response in most CHF patients (Fig. 2), suggesting that estimated fractional O_2 extraction increased above the steady-state level because of impaired muscle blood flow relative to $\dot{V}O_2$ (3, 22, 23, 57). Interestingly, this pattern of response is qualitatively similar to the undershoot in the capillary PO_2 responses previously observed in the exercising muscle of diabetic (54) and CHF animals (5, 6, 18, 35) and identical to the $\Delta[\text{deoxy-Hb+Mb}]$ profiles described in patients with Type 2 diabetes (3) and chronic obstructive pulmonary disease (11). This specific pattern of response is thought to be related to a transient lowering of capillary PO_2 that seems to be large enough to reduce the diffusion gradient from capillary to mitochondria thereby impairing O_2 flux and constraining the rate of increase in muscle $\dot{V}O_2$ (22, 23, 57).

Our results add novel information to previous studies that used NIRS-based measurements during incremental (65) or small muscle mass exercise (44) in patients with CHF. In fact, the single study that has looked at the kinetics of $\Delta[\text{deoxy-Hb+Mb}]$ at the onset of moderate-intensity exercise (40) evaluated CHF patients after heart transplantation. Interestingly, these authors did not find significant differences in $\Delta[\text{deoxy-Hb+Mb}]$ kinetics in recipients vs. normal controls, despite slower $\dot{V}O_{2p}$ kinetics in patients (40). These findings suggest that the metabolic abnormalities in the skeletal muscles were the main mechanism leading to slower $\dot{V}O_{2p}$ kinetics in their subjects which is at marked variance with the present

findings in less severe patients. Conversely, our data are consistent with previous animal studies that suggest that the behavior of PO_{2mv} (and, conceivably, $\Delta[\text{deoxy-Hb+Mb}]$ on the inverse direction) is critically influenced by disease severity in rats with CHF, i.e., faster PO_{2mv} kinetics associated with a signal undershoot in moderate CHF and slower PO_{2mv} dynamics without undershoots in more advanced CHF (6, 18). These findings were interpreted as evidence that severe CHF has been associated with proportional impairments in $\dot{Q}O_{2mv}$ and muscle oxidative metabolism with the net effect being slower rather than faster rates of change in PO_{2mv} (6, 18).

There are several putative explanations by the persistently abnormal $\dot{Q}O_{2mv}$ kinetics at the onset of exercise despite optimal medical therapy. Firstly, QT kinetics were significantly slower in CHF patients than controls (Fig. 1, Table 2). In this context, the strong cardiac β_2 -blocking effect of carvedilol was likely to be instrumental (19) because MRT-HR was $\sim 80\%$ lower in patients than controls. A study with "old," nonselective β -blockers did find a slowing effect on-exercise $\dot{V}O_{2p}$ kinetics (30), and Guazzi and Agostoni (29) reported that carvedilol failed to accelerate $\dot{V}O_{2p}$ kinetics in moderately impaired patients with CHF. In fact, despite positive effects on mortality (53), most of the large randomized controlled trials actually failed to demonstrate a significant effect of newer β -blockers upon submaximal exercise tolerance (19). The positive effects of carvedilol-related α -adrenergic blockade on vascular tone might have also vanished over time (37). Noteworthy, patients' therapy had been optimized according to current clinical guidelines (17, 32) that do not include a formal assessment of pulmonary gas-exchange kinetics to titrate the prescribed doses of medication. Consequently, we cannot rule out that would be necessary higher doses of ACEIs and ARBs to counterbalance the potentially deleterious effects of β -blockade in the $\dot{Q}O_{2mv}$ dynamics at the on-exercise transient. Secondly, despite potential improvements in central cardiovascular performance, pharmacological treatment may have failed to ameliorate the impairment in muscle microvascular function in CHF (49, 55). In fact, a recent study combining NIRS and ^{31}P magnetic resonance spectroscopy found that the recovery kinetics of $[\text{deoxy-Hb+Mb}]$ were slower than that of phosphocreatine after single-leg extension exercise in well-treated New York Heart Association class II–III patients (34). These findings suggest that impaired microvascular function might have contributed to limit muscle O_2 availability because the exercise paradigm was not associated with substantial increases in the central cardiovascular demands. Finally, patients were submitted to supra-GET exercise, thereby predisposing $\dot{V}O_{2p}$ kinetics to be delivery limited (56). However, this exercise intensity domain was deemed the most adequate to test the main study hypothesis since it would pose a higher-than-usual burden to the cardiovascular system under treatment. In fact, despite the exercise test has been performed at submaximal intensities, $\dot{V}O_{2p}$ at Tim was quite similar to peak $\dot{V}O_{2p}$ (Table 1), suggesting the development of a marker of heavy-intensity exercise, i.e., the $\dot{V}O_{2p}$ "slow" component (56).

Methodological Considerations and Interpretative Issues

Because of the cross-sectional and noninvasive nature of the present investigation, several methodological and interpreta-

tive aspects merit further clarification. We, like others (14, 22, 23, 28), assumed that the kinetics of $\Delta[\text{deoxy-Hb+Mb}]$ measured at a single site reflects the time course of muscle fractional O_2 extraction following the onset of exercise. However, there exists substantial heterogeneity on the distribution of muscle blood flow and $\dot{V}\text{O}_2$ (36) that might be more relevant in the poorly perfused muscles of CHF patients. Consequently, it is unlikely that a single-site evaluation provides a full depiction of the complete range of individual intramuscular $\dot{Q}\text{O}_{2\text{mv-t0}}\text{-}\dot{V}\text{O}_2$ relationships. It should also be acknowledged that the lowering effect of CHF on capillary O_2 driving pressure is less prominent in fast- rather than slow-twitch fibers (5). Considering the higher proportion of fast-twitch fibers in the quadriceps of the elderly (6) and patients with CHF (5), we may have underestimated the speeding effect of CHF on the rate of increase in muscle fractional O_2 extraction.

A key argument in favor of the $\Delta[\text{deoxy-Hb+Mb}]$ response as a noninvasive surrogate of fractional O_2 extraction dynamics is the similar characteristics of $\Delta[\text{deoxy-Hb+Mb}]$ changes compared with fractional O_2 extraction dynamics calculated in computer simulations (23) and measured in skeletal muscles (27). However, no previous study has confirmed these assumptions in patients with CHF. Another point of concern is the potential interpopulation differences in the relative contribution of Mb to the $\Delta[\text{deoxy-Hb+Mb}]$ signal (42, 64), which might have also impacted on the magnitude and rate of change in muscle deoxygenation. In this context, Lai et al. (38), using a systems biology approach, reported that the Mb contribution to the whole NIRS signal is particularly relevant during hypoxia compared with normoxia. Assuming that the skeletal muscles contract under more hypoxic conditions in CHF patients than healthy controls, we cannot rule out that the Mb contribution to $\Delta[\text{deoxy-Hb+Mb}]$ was higher in patients. However, Mb has lower P_{50} values than Hb, an effect that would tend to slow, not accelerate (Table 2, Fig. 2), the rate of muscle deoxygenation in the CHF patients.

We used the kinetics of the primary component of $\dot{V}\text{O}_{2\text{p}}$ response as an indicator of the muscle $\dot{V}\text{O}_2$ response (2, 25). However, it should be acknowledged that the fitting of a single exponential, though statistically justifiable, is not evidence of similar metabolic mechanisms in the two populations, especially during heavy-intensity exercise. More specifically, it is unlikely that the relative contribution of anaerobic glycolysis to ATP regeneration was equivalent in patients and controls (56). We also recognize that slowing of muscle blood flow may create a temporal dissociation between muscle and pulmonary $\dot{V}\text{O}_2$ kinetics, with the $\dot{V}\text{O}_{2\text{p}}$ response becoming faster than the muscle $\dot{V}\text{O}_2$ dynamics because of changes in the leg-to-lung transit delay (2). Accordingly, we may have underestimated the slowness of muscle $\dot{V}\text{O}_2$ kinetics in CHF patients performing heavy-intensity exercise. Our investigative approach, therefore, used noninvasive methods and was based on several assumptions; consequently, we could only infer the rate of muscle O_2 delivery.

There are some clinical considerations that should be stressed to avoid a widespread extrapolation of our results. Several investigators reported that the likelihood of severe intramyocyte disturbances is increased in patients with end-stage disease (33, 40) and rats with severe CHF (6, 18). Considering that our patients were only moderately impaired (despite severe LV dysfunction by echodopplercardiography

(Table 1), it remains to be tested whether the present results hold true for humans with more advanced disease. However, our sedentary patients had never been submitted to cardiac rehabilitation, predisposing them to severe impairment in muscle oxidative metabolism. We also admit that the response overshoot in $\Delta[\text{deoxy-Hb+Mb}]$ (or $\text{PO}_{2\text{mv}}$ undershoot) is more likely to be found in older subjects (6, 20) than those evaluated in the present study (Table 1). Therefore, our results should be viewed under the perspective that the aging process underlies the behavior of $\Delta[\text{deoxy-Hb+Mb}]$ and $\dot{V}\text{O}_{2\text{p}}$ in both groups and further studies are warranted to confirm the present findings in younger CHF patients. In relation to the fitting approach to $\Delta[\text{deoxy-Hb+Mb}]$ overshoot, it needs to be stressed that a single monoexponential model was used merely for convenience of comparisons and a higher-order model might have better described the observed response profile (Fig. 2).

According to current guidelines, no patient in the present study had clinical indication for resynchronization therapy or LV assist device; nevertheless, it remains to be tested whether the add-on therapy with these nonpharmacological strategies would positively impact on (estimated) $\dot{Q}\text{O}_{2\text{mv}}$ kinetics. Finally, care should be taken to extrapolate our results for patients with CHF secondary to ischemic heart disease since CHF etiology may impact on the determinants of exercise tolerance in this patient population (13).

Conclusions

The dynamic matching between O_2 delivery to, and O_2 uptake by, the peripheral muscles is significantly impaired at the transition to heavy-intensity exercise in patients with CHF who had been adequately treated with the best-available pharmacological therapy. These abnormalities are closely related to the derangements on the central cardiovascular adjustments to exertion. Our data, therefore, indicate that despite the remarkable advances in clinical management of CHF, disturbances in the cardiocirculatory responses still play a prominent role in limiting $\dot{V}\text{O}_{2\text{p}}$ kinetics and tolerance to heavy-intensity exercise in humans with naturally occurring forms of the disease.

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Abstract

Impaired muscle blood flow at the onset of heavy-intensity exercise may transiently reduce microvascular O_2 pressure and decrease the rate of O_2 transfer from capillary to mitochondria in chronic heart failure (CHF). However, advances in the pharmacological treatment of CHF (e.g., angiotensin-converting enzyme inhibitors and third generation of β -blockers) may have improved microvascular O_2 delivery to an extent that intramyocyte metabolic inertia might become the main locus of limitation of O_2 uptake ($\dot{V}O_2$) kinetics. We included 10 optimally treated sedentary patients (ejection fraction = $29 \pm 8\%$) and 11 age-matched controls. We assessed the rate of change of pulmonary $\dot{V}O_2$ ($\dot{V}O_{2p}$), tissue O_2 extraction in the vastus lateralis estimated by concentration of deoxy-hemoglobin+myoglobin ($-\Delta[\text{deoxy-Hb+Mb}]$) measured by near-infrared spectroscopy (NIRS), and cardiac output (\dot{Q}_T) during high-intensity exercise performed to the limit of tolerance (T_{lim}). Sluggish $\dot{V}O_{2p}$ and \dot{Q}_T kinetics in patients were significantly related to lower T_{lim} values ($P = 0.05$). The dynamics of $\Delta[\text{deoxy-Hb+Mb}]$ were faster in patients than controls (mean response time (MRT) = 15.9 ± 2.0 s vs. 19.0 ± 2.9 s; $P = 0.05$) with a subsequent response “overshoot” being found only in patients (7/10). Moreover, $\tau\dot{V}O_{2p}/MRT-\Delta[\text{deoxy-Hb+Mb}]$ ratio was greater in patients (4.69 ± 1.42 s vs. 2.25 ± 0.77 s; $P = 0.05$) and related to \dot{Q}_T kinetics and T_{lim} ($R = 0.89$ and 0.78 , respectively; $P = 0.01$). We conclude that despite the advances in the pharmacological treatment of CHF, disturbances in “central” and “peripheral” circulatory adjustments still play a prominent role in limiting $\dot{V}O_{2p}$ kinetics and tolerance to heavy-intensity exercise in nontrained patients.

Key-words: blood flow; chronic heart failure; hemodynamics; near-infrared spectroscopy; oxygen consumption

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