Blutvolumen-Veränderungen während Ausdauer- und Kraftbelastungen und ihre Bedeutung für die Leistungsfähigkeit

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INHALTSVERZEICHNIS

ABKÜRZUNGSVERZEICHNIS

$avDO_2$	arterio-venöse Sauerstoffdifferenz
BV	Blutvolumen
CaO_2	arterieller Sauerstoffgehalt
CO	Kohlenmonoxid
EDV	End-diastolisches Volumen
ESV	End-systolisches Volumen
EZV	Erythrozytenvolumen
[Hb]	Hämoglobinkonzentration
Hbmass	Hämoglobinmasse
$[HCO_3^-]$	Hydrogenkarbonatkonzentration
Hct	Hämatokrit
HF	Herzfrequenz
$[La^-]$	systemische Laktatkonzentration
La^-	systemische Laktatmenge
LV	Links ventrikulär
O_2	Sauerstoff
pO_2	Sauerstoffpartialdruck
pCO_2	Kohlenstoffdioxidpartialdruck
PV	Plasmavolumen
$\dot{Q}$	Herzminutenvolumen
SV	Schlagvolumen
ScO_2	kapilläre Sauerstoffsättigung
$\dot{V}E$	Ventilation
$\dot{V}O_2$	Sauerstoffaufnahme
$\dot{V}O_{2max}$	maximale Sauerstoffaufnahme
β_{bi}	Bikarbonatpufferung
β_{nbi}	Nicht-Bikarbonatpufferung
β_{tot}	Gesamtpufferkapazität

ABBILDUNGSVERZEICHNIS

TABELLENVERZEICHNIS

I honour, and shall always honour, every one who advances the noble science of physiology.

- Charles Darwin in einem Brief an Professor A. F. Holmgren am 14. April 1881.

1 Einleitung

Das Blut ist ein fließendes Organ und macht bei einem erwachsenen Menschen ca. 6-8 % der Körpermasse aus *(1)*. Zu den vielfältigen Eigenschaften und Funktionen des Blutes zählen zum Beispiel der Transport von Atemgasen, wie Sauerstoff und Kohlendioxid, die Verteilung von Nährstoffen und Metaboliten, wie Glukose oder Laktat, sowie die Aufrechterhaltung der homöostatischen Milieufunktion, was sich in der Konstanthaltung des pH-Werts äußert *(2)*.

Es ist seit langem bekannt, dass ein systematisches Ausdauertraining zu einer substantiellen Erhöhung der Gesamtmenge an Blut im Körper führt, wodurch die eingangs erwähnten Funktionen optimiert werden *(3)*. Dies ist in erster Linie mit einer Steigerung der maximalen Sauerstoffaufnahme ($\dot{V}O_{2max}$), einer der wichtigsten Determinanten der Ausdauerleistungsfähigkeit, assoziiert *(4,5)*. Der besondere Einfluss des Blutvolumen (BV) wird hierbei durch das Fick'sche Prinzip verdeutlicht, welches die $\dot{V}O_{2max}$ als das Produkt aus Herzminutenvolumen ($\dot{Q}$) und arterio-venöser Sauerstoffdifferenz ($avDO_2$) bildet. Hier reguliert das BV über das Ausmaß des venösen Rückstroms nicht nur $\dot{Q}$, sondern bildet über die Gesamthämoglobinmenge (Hbmass) und die Sauerstofftransportkapazität auch die Basis für eine möglichst hohe $avDO_2$ *(6)*. Es ist zudem bekannt, dass das dem Kreislauf zur Verfügung stehende BV während muskulärer Belastung aufgrund von Flüssigkeitsverschiebungen mit zunehmender Intensität sukzessive abnimmt. Es bleibt jedoch offen, ob sich das Ausmaß dieser Flüssigkeitsverschiebungen zwischen unterschiedlichen Trainingsformen, z. B. Ausdauer- oder Kraftbelastungen unterscheidet und welchen generellen Einfluss diese auf die sportliche Leistungsfähigkeit besitzen.

Vor allem im Ausdauertrainings ist eine Zunahme der $\dot{V}O_{2max}$ zusätzlich mit morphologischen Veränderungen des Herzmuskels in Verbindung gebracht, denen eine harmonische Dilatation aller Herzhöhlen zugrunde liegt. Ursächlich für diese myokardiale Adaptation ist wahrscheinlich eine erhöhte Volumenbelastung, die im engen Zusammenhang mit dem BV steht *(7)*. Allerdings ist bis heute nicht abschließend geklärt, in welchem integralen Zusammenhang die $\dot{V}O_{2max}$ und die Herzdimensionen stehen und welche Rolle dabei letztlich dem BV zukommt.

Im Rahmen dieser Arbeit erfolgt zunächst eine ganzheitliche Betrachtung des kardiopulmonalen Systems und dessen Relevanz für die Ausdauerleistungsfähigkeit unter besonderer Berücksichtigung des Blutvolumens. Darauf folgt eine Beschreibung der angewandten Methoden zur Bestimmung von Hämoglobinmenge und Blutvolumen sowie des Herzminutenvolumens. Im Anschluss werden die damit zusammenhängenden Studien mit Fragestellungen und Ergebnissen erläutert, bevor sie in einer zusammenfassenden Synopse diskutiert werden.

2 Theoretische Vorbetrachtungen

2.1 Biologische Determinanten der Ausdauerleistungsfähigkeit

Die Ausdauerleistungsfähigkeit ist von einer Vielzahl von biologischen Faktoren abhängig, die durch systematisches Training unterschiedlich stark beeinflusst werden können. Zu diesen Faktoren zählen die sog. Laktatschwelle, der Sauerstoffverbrauch, der nötig ist, um eine bestimmte Wettkampfleistung oder -geschwindigkeit zu produzieren (auch Ökonomie oder Effizienz) sowie die maximale Sauerstoffaufnahme *(4,8)*. Diese Faktoren werden in *Abbildung 1* zusammengefasst, wobei zusätzlich angezeigt ist, welches Potenzial bei bereits ausdauertrainierten Personen besteht, diese Faktoren weiter zu optimieren *(9)*.

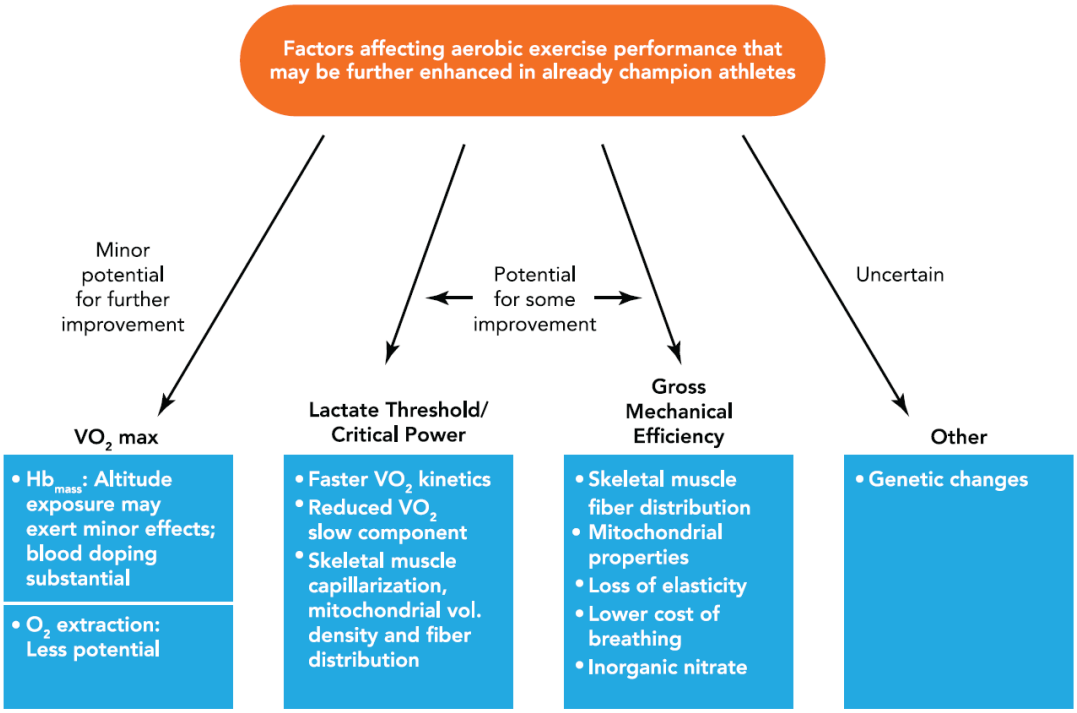

Abbildung 1. Faktoren, die sich auf die aerobe Leistungsfähigkeit auswirken und die bei bereits erfolgreichen Sportlern noch verbessert werden können *(9)*.

Beim Konzept der Laktatschwelle geht man von einem kurvilinearen Zusammenhang zwischen Laktatkonzentration ([La^-]) und der Intensität einer Belastung respektive der metabolischen Beanspruchung aus *(10)*. Entsprechend kann die Rate des aeroben Metabolismus anhand der [La^-] abgeschätzt werden. Würde beispielsweise die mechanische Leistung auf einem Fahrradergometer sukzessive erhöht werden, so fände man bei untrainierten Personen eine stabile [La^-]

bis circa 60 % der $\dot{V}O_{2max}$. Bei ausdauertrainierten Personen kann diese Schwelle auf über 75 % ansteigen *(11)*. Während die physiologische Regulation der Laktatschwelle äußerst komplex ist, so wird sie doch hauptsächlich von der oxidativen Kapazität der Skelettmuskulatur bestimmt. Bei Elite-Athleten nimmt diese Kapazität um das mehr als Zweifache zu, was eng mit einer Rechtsspreizung der Laktatkurve verknüpft ist *(12)*.

In Bezug auf die Ökonomie bzw. Effizienz geht es um die Frage, welche Laufgeschwindigkeit oder mechanische Leistung von einem Individuum bei einem bestimmten Sauerstoffverbrauch generiert werden kann. Beim Fahrradfahren bei einer festgelegten mechanischen Leistung (300 Watt) kann die mechanische Effizienz bei Ausdauertrainierten zwischen 18 und 24 % variieren *(13)*. Mehr als die Hälfte dieser Variabilität ist dem Anteil an Typ I Muskelfasern in der Zielmuskulatur zuzuschreiben. Muskelphysiologisch kann konstatiert werden, dass die Effizienz, mit der chemische Energie aus der Hydrolyse von Adenosintriphosphat in physikalische Arbeit umgewandelt werden kann, in hohem Maße von der Verkürzungsgeschwindigkeit der Sarkomere abhängig ist *(8)*. Da Typ I Muskelfasern diesbezüglich eine größere mechanische Effizienz aufweisen, ist es nicht verwunderlich, dass Ausdauersportler*innen einen deutlich höheren Anteil dieser Fasertypen besitzen *(14,15)*. Zwar spielt die mitochondriale Kapazität in Bezug auf die Effizienz ebenfalls eine wichtige Rolle, allerdings sind sowohl Typ I als auch Typ II Fasern im gleichen Ausmaß in der Lage diese zu erhöhen, was die Wichtigkeit der mechanischen Effizienz der Typ I Fasern nochmals hervorhebt.

Im Gegensatz dazu ist die maximale Sauerstoffaufnahme in erster Linie von der Sauerstofftransportkapazität des kardiopulmonalen Systems abhängig, also vom Herzminutenvolumen und der Gesamthämoglobinmenge (Hbmass) im Körper. Da unter den aufgeführten biologischen Determinanten der Ausdauerleistungsfähigkeit die $\dot{V}O_{2max}$ von besonderer Wichtigkeit ist und im Rahmen dieses Projekts eine zentrale Kenngröße bildet, wird sie im Folgenden ausführlicher beleuchtet.

Die maximale Sauerstoffaufnahme

Die maximale Sauerstoffaufnahme ($\dot{V}O_{2max}$) beschreibt diejenige Menge an Sauerstoff, die bei schwerer körperlicher Arbeit und unter dem Einsatz großer Muskelgruppen durch das kardiopulmonale System aufgenommen und zu den arbeitenden Muskeln transportiert werden kann. Sie wird durch das Fick'sche Prinzip zum Ausdruck gebracht, welches sich aus dem Produkt von Schlagvolumen (SV), Herzfrequenz (HF) und arterio-venöser Sauerstoffdifferenz ($avDO_2$) zusammensetzt. Das Produkt aus SV und HF wird weiterhin als Herzminutenvolumen ($\dot{Q}$) be-

zeichnet. *Abbildung 2* veranschaulicht das Fick'sche Prinzip und die zugrundeliegenden physiologischen Adaptationen, die zu einer Erhöhung der $\dot{V}O_{2max}$ durch systematisches Training führen *(5)*. Auf Basis dieser Gleichung ist ersichtlich, dass eine Steigerung jedweder Komponente zu einer Zunahme der $\dot{V}O_{2max}$ führen kann.

Dabei steht die $avDO_2$ für das Ausmaß der Sauerstoffextraktion in der O_2-Transportkette. Eine Verbesserung der Sauerstoffextraktion ist auf eine gesteigerte Muskelperfusion und -diffusion sowie eine erhöhte mitochondriale Kapazität zurückzuführen *(16)*. Heutzutage ist allerdings bekannt, dass die $avDO_2$ nur einen geringen Einfluss auf trainingsbedingte Zunahmen der $\dot{V}O_{2max}$ hat *(17)*. Auch für die maximale HF konnte gezeigt werden, dass diese sich durch Training nicht verändert bzw. sogar leicht abfallen kann *(18)*. Entsprechend bildet das SV die wichtigste Determinante in Bezug auf eine Steigerung der $\dot{V}O_{2max}$. Dabei ist bekannt, dass ausdauertrainierte Personen im Vergleich zu untrainierten in der Regel ein deutlich höheres maximales SV generieren können *(19,20)*. Weitaus weniger ist allerdings über den Verlauf der SV-Antwort während einer dynamischen Muskelarbeit bis zur Erschöpfung bekannt. Wissenschaftler*innen debattieren seit Jahren darüber, ob das SV bereits vor Erreichen der $\dot{V}O_{2max}$ grundsätzlich ein Plateau bildet oder ob lediglich Ausdauersportler*innen in der Lage sind, das SV bis zur $\dot{V}O_{2max}$ zu steigern *(21,22)*.

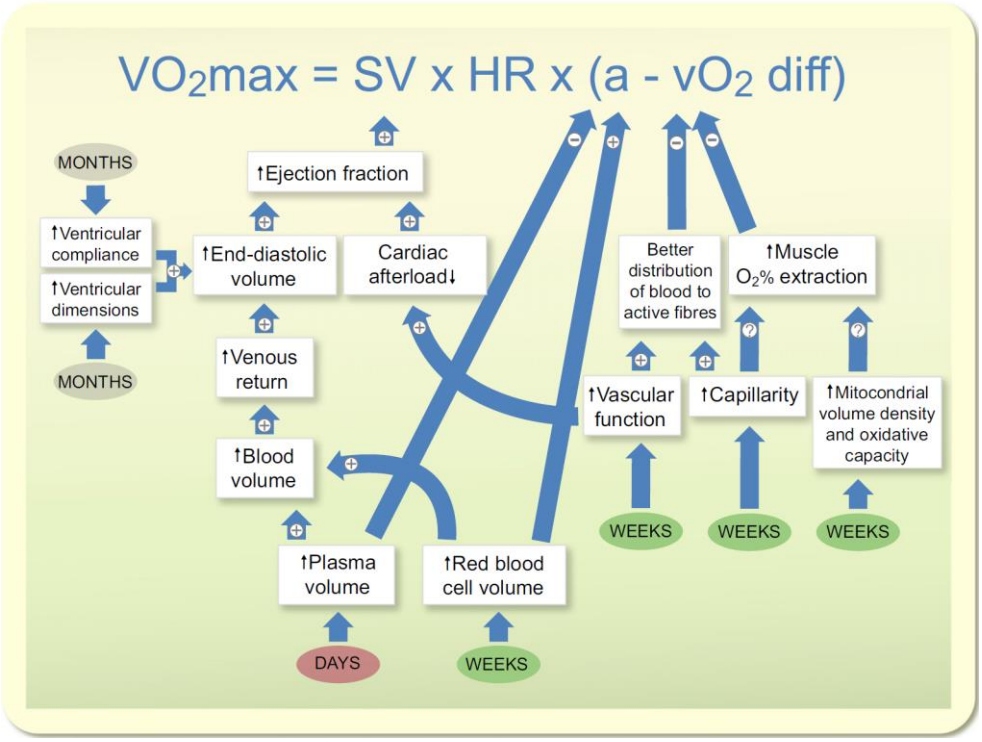

Abbildung 2. Zugrundeliegende physiologische Adaptationen die zu einer Erhöhung der maximalen Sauerstoffaufnahme ($\dot{V}O_{2max}$) durch systematisches Training führen *(5)*.

Bei genauer Betrachtung der in *Abbildung 2* aufgeführten Adaptationen wird weiterhin deutlich, dass das SV neben der vaskulären Funktion vor allem vom vorhandenen BV abhängig ist. Dabei werden durch systematisches Ausdauertraining sowohl die zellulären (d.h. das Erythrozytenvolumen, EZV), als auch die flüssigen Bestandteile, also das Plasmavolumen (PV) substantiell erhöht. Im Vergleich zur O_2-Extraktion tragen diese beiden Komponenten in besonderem Maße über eine Steigerung des Herzminutenvolumens und der Sauerstofftransportkapazität zu einem Anstieg der $\dot{V}O_{2max}$ bei *(5)*. Dabei wurde festgestellt, dass in Normoxie die O_2-Transportkapazität mit einem Anteil von 70-75 % der maßgeblich limitierende Faktor der $\dot{V}O_{2max}$ ist *(16)*. Die restlichen 25-30 % verteilen sich entsprechend auf die O_2-Extraktion, also Muskelperfusion und -diffusion sowie die mitochondriale Kapazität.

Eine Kenntnis über das Ausmaß der Sauerstofftransportkapazität während körperlicher Belastung ist demnach von übergeordneter Wichtigkeit. Über eine Multiplikation von $\dot{Q}$ mit dem arteriellen Sauerstoffgehalt − der anhand der Hämoglobinkonzentration ([Hb]) und der Sauerstoffsättigung in einer Blutprobe zu bestimmen ist − kann die O_2-Transportkapazität des kardiopulmonalen Systems in Milliliter pro Minute berechnet werden. Die [Hb] ist dabei abhängig von der Gesamthämoglobinmenge (Hbmass) als Bestandteil des EZV und dem Plasmavolumen (PV). Während der Anteil des im Plasma transportierten Sauerstoffs trivial ist (~0,3 mL O_2 pro 100 mL Plasma), bindet jedes Gramm Hämoglobin, das in den Erythrozyten enthalten ist, 1,39 mL Sauerstoff (Hüfner-Zahl). Infolgedessen ist die Beziehung zwischen $\dot{V}O_{2max}$ und Hbmass stärker als die zwischen der $\dot{V}O_{2max}$ und der [Hb] *(23,24)*. Änderungen in der $\dot{V}O_{2max}$ sind demnach proportional zu den Änderungen im arteriellen Sauerstoffgehalt und der O_2-Transportkapazität. Hier konnte gezeigt werden, dass eine Änderung der Hbmass um 1 g mit einer Änderung der $\dot{V}O_{2max}$ um 4 $mL \cdot min^{-1}$ verbunden ist *(25)*. Die bei Elite-Ausdauersportler*innen vorliegenden Werte der Hbmass sind dabei 40-50 % höher als bei untrainierten Vergleichspersonen und liegen für Frauen bei ~12 $g \cdot kg^{-1}$ und für Männer bei ~15 $g \cdot kg^{-1}$. Neben der Zunahme des EZV kommt es auch zu einer Zunahme des PV, was sich in einem erhöhten totalen BV bemerkbar macht. Ein erhöhtes BV stellt eine der wichtigsten Voraussetzungen für ein höheres SV respektive $\dot{Q}$ bei diesen Personen dar. So erreichen beispielsweise männliche Elite-Ausdauersportler ein mittleres maximales Herzminutenvolumen von über 35 $L \cdot min^{-1}$, was über ein SV von 190 mL realisiert wird *(26)*. Diese Zahlen verdeutlichen, dass $\dot{Q}$ die Grundlage für eine erhöhte O_2-Transportkapazität und somit $\dot{V}O_{2max}$ im Ausdauersport bildet.

Neben den hämodynamischen Einflussgrößen weisen ausdauertrainierte Personen aber auch regelmäßig strukturelle und funktionelle Anpassungen des Myokards auf. Bereits am Ende des 19. Jahrhunderts konnten bei Skilangläufern Vergrößerungen der Herzmuskulatur festgestellt

werden, die im Nachgang echokardiographisch bestätigt wurden *(27,28)*. Heutzutage beschreibt man diesen Zustand als exzentrische Myokardhypertrophie, die durch eine gesteigerte linksventrikuläre (LV) Compliance und reduzierte vaskuläre Resistenz bzw. verminderte Nachlast charakterisiert ist *(29–31)*. Diese myokardialen Anpassungen tragen ebenfalls zu einer Steigerung des SV während körperlicher Aktivität bei. Es bleibt aber bis heute spekulativ, ob sie auch das Resultat einer chronisch erhöhten Volumenbelastung sind, die mit einem erhöhten Zentralvenendruck einhergeht und durch ein hohes BV bedingt ist *(32)*. Dies liegt vor allem daran, dass in den meisten Studien das BV und die kardialen Dimensionen jeweils unabhängig voneinander in ihrem Einfluss auf die Ausdauerleistungsfähigkeit untersucht wurden.

2.2 Plasmavolumenveränderungen während körperlicher Belastung

Das BV passt sich durch die Zunahme im PV und EZV nicht nur mittel- und langfristig an ein Ausdauertraining an, sondern ist auch akut von teils hohen Schwankungen betroffen. Diese können unter anderem durch Änderungen der Körperposition, des Hydratationszustands oder dynamische Muskelarbeit provoziert werden *(33–35)*. Frühere Untersuchungen haben bei kurzzeitigen, hoch-intensiven sowie langandauernden, aeroben Belastungen eine Abnahme des PV im Bereich von 5-22 % feststellen können *(36–40)*, wobei diese Werte in den meisten Fällen indirekt über eine Bestimmung der [Hb] und des Hämatokrit (Hct) ermittelt wurden. Erklärbar sind diese Abnahmen durch eine größere Filtrationsrate, einen Anstieg des Blutdrucks, eine erhöhte Schweißproduktion sowie eine Akkumulation von osmotisch wirksamen Substanzen innerhalb der Muskelzelle, zum Beispiel Laktat oder Phosphat. Letztere führen zu signifikanten Flüssigkeitsverschiebungen vom extra- in den intrazellulären und interstitiellen Raum *(41,42)*.

Geht man von den bisher geschilderten physiologischen Grundlagen aus, so sollte die belastungsinduzierte Abnahme des PV und damit einhergehend des BV einen nachteiligen Effekt auf das SV respektive $\dot{Q}$ und somit die $\dot{V}O_{2max}$ besitzen. Gleichzeitig führt die Abnahme des PV aber auch zu einem Anstieg der [Hb]. Dadurch könnte unter Berücksichtigung der O_2-Sättigung und $\dot{Q}$ dieser nachteilige Effekt auf die O_2-Transportkapazität möglicherweise kompensiert werden. Es existieren bis heute nur sehr wenige Daten, die sich mit Volumenveränderungen während Ausdauer- und Kraftbelastungen beschäftigt haben und die meisten Studien berichten zudem nur prozentualen Abnahmen, die auf Basis der [Hb] und des Hct berechnet wurden *(36,38)*. Entsprechend ist es auch nicht verwunderlich, dass die in diesem Abschnitt beschriebenen Effekte der Volumenveränderungen auf das SV oder die Sauerstofftransportkapazität bis dato noch nicht untersucht wurden.

Der durch die PV-Veränderung bedingte Anstieg der [Hb] und des Hct zeigt aber auch, dass im Blut gemessene Parameter bzw. Konzentrationsangaben grundsätzlich von der Höhe des PV abhängig sind, das als Distributionsmedium fungiert. Frühere Untersuchungen konnten zum Beispiel feststellen, dass eine belastungsinduzierte PV-Abnahme zu signifikant höheren Cholesterin-, Natrium-, Magnesium- und Glukosekonzentrationen führte *(43–46)*. Auf Basis dieser Ergebnisse forderte man Konzentrationsangaben von im Blut gemessenen Stoffen für mögliche PV-Veränderungen zu korrigieren *(47)*, was aber bis heute kaum durchgeführt wird.

In der Sportmedizin bildet die Laktatkonzentration ([La^-]) einen wichtigen metabolischen Marker und die Kinetik der [La^-] im Verlauf eines inkrementellen Ausbelastungstests bildet standardmäßig eine Grundlage für die Bewertung der Ausdauerleistungsfähigkeit und ermöglicht Trainingsempfehlungen *(48,49)*. Theoretisch könnte das BV nun an zwei Stellen ansetzen, um einen Einfluss auf die gemessenen [La^-] zu nehmen: Erstens chronisch durch die trainingsbedingte Hypervolämie, die grundsätzlich zu niedrigeren [La^-] führen sollte und zweitens akut durch belastungsbedingte PV-Veränderungen, die, in Abhängigkeit der systemischen Laktatmenge (La^-), höhere [La^-] provozieren sollten. Da es wie bereits erwähnt durch Ausdauertraining nicht nur zu einer substantiellen Erhöhung des BV, sondern auch zu einer veränderten Laktatkinetik kommt, ist die Untersuchung dieser Mechanismen von besonderer Bedeutung.

2.3 Bestimmung der Hämoglobinmenge und des Blutvolumens

Die Bestimmungen von Hbmass und BV beruhen i. d. R. auf Indikator-Verdünnungsmethoden. Dabei werden die Erythrozyten oder Plasmaproteine mit einem Tracer markiert, deren im Anschluss gemessene Konzentration unter Berücksichtigung des injizierten Volumens Rückschlüsse auf das Gesamtvolumen der Erythrozyten bzw. des Plasmas zulassen. Eine in der Sportmedizin häufig eingesetzte Methode zur Bestimmung der Hbmass ist die sog. optimierte Kohlenmonoxid-Rückatmungsmethode *(50,51)*. Diese minimal-invasive, kostengünstige und valide Methode nutzt Kohlenmonoxid (CO) als Marker für das Hämoglobin und kam bei allen vorliegenden Studien zum Einsatz, weshalb sie nachfolgend beschrieben wird.

Um eine gleichmäßige Blutverteilung und damit eine standardisierte [Hb] zu erhalten, verbleiben die Teilnehmer*innen für mindestens 10 Minuten vor Beginn des Tests in sitzender Position. Anschließend werden die Testpersonen gebeten, ein Gasgemisch bestehend aus einem CO-Bolus und medizinischem Sauerstoff (O_2) in einem geschlossenen System für zwei Minuten zu atmen. Die Menge des inhalierten CO-Bolus orientiert sich dabei an der Körpermasse sowie dem Trainingszustand und liegt zwischen 0,7 und 1,0 $mL \cdot kg^{-1}$.

Im Vorfeld der Rückatmung sowie in der 6. und 8. Minute des Testablaufs werden jeweils zwei Kapillaren arterialisierten Blutes aus dem Ohrläppchen entnommen, um das Carboxyhämoglobin (COHb) zu analysieren. Anhand eines CO-Analysators wird die Menge an CO, die während der Inhalationsphase nicht aufgenommen wird, im Spirometer bestimmt und es wird berechnet, wieviel CO direkt nach dem Test abgeatmet wird. Dazu wird die Differenz zwischen der endexspiratorischen CO-Konzentration vor und in der vierten Minute nach Beginn des Tests bestimmt. Die Berechnung der Hbmass erfolgt anschließend anhand von folgender Formel:

$$Hbmass\ (g) = K \times MCO\ (mL) \times 100 \times (\Delta COHb\ (\%) \times 1{,}39)^{-1} \quad (1)$$

Formel 1. Berechnung der Gesamthämoglobinmenge.

Darin bildet

- K = Korrekturfaktor:

$Barometrischer\ Luftdruck \div (760 \times (1 + (0{,}003661 \times Temperatur\ in\ °C\ )))$

- MCO = Kohlenmonoxid (CO) in mL im Blutkreislauf:

$CO_{gegeben} - CO_{Rest\ im\ System} - CO_{abgeatmet} - CO_{Myoglobin}$

- ΔCOHb (%) = Prozentuale Differenz zwischen dem Ausgangswert und dem Mittelwert des COHb aus der 6. und 8. Minute in der Blutprobe nach der CO-Verabreichung
- 1,39 = Hüfner'sche Zahl (mL $O_2 \cdot g^{-1}$ Hb)

Auf Basis der Hbmass, der [Hb] und des Hct können anschließend das Blutvolumen (BV), Erythrozytenvolumen (EZV) sowie das Plasmavolumen (PV) berechnet werden. Diese Berechnungen waren ein integraler Bestandteil aller Studien, um das absolute BV zu einer bestimmten Belastungsintensität bzw. einem bestimmten Zeitpunkt zu berechnen. Dadurch konnten im Anschluss die belastungsinduzierten BV-Veränderungen quantifiziert werden.

$$BV\ (mL) = Hbmass\ (g) \times 100 \div [Hb]\ (g \cdot \mathrm{dL}^{-1}) \div 0{,}91 \quad (2)$$

Formel 2. Berechnung des Blutvolumens (BV) auf Basis der Gesamthämoglobinmenge (Hbmass) und der Hämoglobinkonzentration ([Hb]).

$$EZV\ (mL) = Hbmass\ (g) \div ([Hb]\ (g \cdot \mathrm{dL}^{-1}) \div Hct \times 100) \times 100 \quad (3)$$

Formel 3. Berechnung des Erythrozytenvolumens (EZV) auf Basis der Gesamthämoglobinmenge (Hbmass), der Hämoglobinkonzentration ([Hb]) und des Hämatokrits (Hct).

$$PV\ (mL) = BV\ (mL) - EZV(mL) \quad (4)$$

Formel 4. Berechnung des Plasmavolumens (PV) auf Basis des Blutvolumens (BV) und des Erythrozytenvolumens (EZV).

In **Formel 2** stellt die dimensionslose Zahl 0,91 den Zellfaktor *F* auf Meereshöhe dar *(52)*. Dieser gibt das Verhältnis des Hct des Gesamtblutes zum Hct des entnommenen Blutes an. Er beträgt in Ruhe im Mittel 0,875 und kann auf 0,903 ansteigen, wobei sich die Werte in der Literatur teilweise minimal unterscheiden *(53,54)*. Da bis heute experimentelle Untersuchungen zur Veränderung des Zellfaktors während schwerer körperlicher Arbeit fehlen, wurde für die Berechnung des BV in den vorliegenden Studien ein festgelegter Zellfaktor verwendet. Hätte man den Zellfaktor für die Berechnung des BV unter Ruhebedingungen jedoch an den in der Literatur beschriebenen Wert von 0,875 adjustiert, so wären z. B. die belastungsinduzierten Plasmavolumenveränderungen und deren Einfluss auf die Sauerstoff- und Laktattransportkapazität noch größer ausgefallen.

Bezüglich der Genauigkeit der optimierten CO-Rückatmungsmethode lässt der typische Fehler Rückschlüsse auf die Reliabilität der Methode zu. Dieser liegt zwischen 1,1 und 2,3 % *(55–58)*. In eigenen Untersuchungen lag der typische Fehler zwischen 1,3 und 1,7 % *(50,59,60)*. Vergleichbar dazu ist der mittlere typische Fehler einer ähnlichen CO-Rückatmungsmethode von Burge & Skinner von 1,7 % *(61)*. Die als sog. Goldstandard geltenden Verdünnungsmethoden mit einem radioaktiven Tracer (^{51}Cr, 2,8 %) sowie andere CO- und Evans Blue Methoden (3,9 respektive 6,7 %) weisen dabei deutlich höhere Ungenauigkeiten auf *(62)*. Somit stellt die optimierte CO-Rückatmungsmethode eine genaue und verlässliche Methode zur Bestimmung der Hbmass dar, vorausgesetzt sie wird von erfahrenen Untersucher*innen und mit modernen Blutgasanalysatoren durchgeführt *(63)*.

2.4 Methoden zur Bestimmung des Herzminutenvolumens

Die Bestimmung des Herzminutenvolumens ($\dot{Q}$) kann sowohl auf invasivem als auch nichtinvasivem Wege erfolgen. Dabei haben sich in der klinischen Medizin invasive Methoden wie

das Fick'sche Prinzip und die Thermodilution als Goldstandrad etabliert *(64)*. Diese Methoden sind allerdings sehr teuer und aufwändig und verlangen eine ärztliche Expertise, was deren praktische Nutzung einschränkt. Nicht-invasive Methoden, wie z. B. Rückatmungsmethoden, bei denen der pulmonale Blutfluss über den Anteil eines abgeatmeten Gases geschätzt wird, bieten sich deshalb als akzeptable Alternative an. Physiologischer Hintergrund ist, dass bei gesunden Menschen die pulmonale Aufnahme eines Gases proportional zum pulmonalen Blutfluss ist *(65)*. Zu den Gasen, die hierbei zum Einsatz kommen, zählen u.a. Acetylen (C_2H_2) oder Distickstoffmonoxid (N_2O). Weiterhin können sog. Inertgase wie Helium (He), Argon (Ar), Methan (CH_4) oder Schwefelhexafluorid (SF_6) dem Gasgemisch hinzugefügt werden *(64)*.

Das Innocor®-System (Innovision, Glamsbjerg, Dänemark) bildet dabei den Goldstandard für die nicht-invasive Messung des Herzzeitvolumens. Mit dem Innocor® atmet jede Versuchsperson ein Gasgemisch ein, das aus 5 % blutlöslichem N_2O, 1 % blutunlöslichem SF_6 und 94 % O_2 besteht und zusammen mit Umgebungsluft in einen Rückatmungsbeutel gefüllt wird. Das Verhältnis aus Prüfgas, Beutelvolumen und Umgebungsluft wird anhand des Tidalvolumens und der Sauerstoffaufnahme bestimmt. Zu jedem Messzeitpunkt wird die Testperson auf die Rückatmung des Testgases in einem geschlossenen Kreislauf umgestellt, innerhalb dessen die Gaskonzentrationen durch photoakustische Analyse quantifiziert werden. Die pulmonale N_2O-Aufnahme wird dabei über die Abnahme von N_2O über drei aufeinanderfolgende Ausatmungen bestimmt, nachdem eine stabile SF_6-Konzentration festgestellt wurde *(66)*. Das Innocor®-System wurde gegenüber der Fick- und Thermodilutionsmethoden validiert und erlaubt entsprechend präzise Bestimmungen von $\dot{Q}$ *(67,68)*. Ein Nachteil bildet jedoch die eingeschränkte Nutzung während körperlicher Aktivität, was sich durch den direkten Eingriff in den Atemrhythmus der Testperson äußert. Außerdem sind mit dem Innocor®-System auch keine kontinuierlichen $\dot{Q}$-Bestimmungen möglich, was z. B. die Interpretation der SV-Antwort erschwert.

Demgegenüber steht mit der transthorakalen Impedanzanalyse eine weitere Möglichkeit zur nicht-invasiven Bestimmung von $\dot{Q}$ zur Verfügung. Hier steht mit dem PhysioFlow Enduro® (Manatec Biomedical, Paris, Frankreich) ein tragbares, batteriebetriebenes und nicht-invasives Herzzeitvolumengerät zur Verfügung, das aus einer elektronischen Einheit besteht, welche mit einer Host-Schnittstelle verbunden ist. Zusätzlich werden zur Erstellung eines Elektrokardiogramms (EKG) insgesamt sechs Elektroden am Oberkörper der Testperson angebracht. Die elektronische Einheit erzeugt einen hochfrequenten Strom mit geringer Amplitude, digitalisiert und verarbeitet das EKG und die modulierten transthorakalen Impedanzsignale. Die Kalkulation des SV basiert dabei auf der Annahme, dass Änderungen im zentralen BV der Aorta ge-

gensätzliche Veränderungen der elektrischen Impedanz induzieren *(69)*. Das PhysioFlow Enduro® erlaubt die kontinuierliche Bestimmung der hämodynamischen Antwort in Ruhe und unter Belastung und liefert somit einen wertvollen Einblick in die individuelle SV-Antwort im Belastungsverlauf.

Im Gegensatz zu anderen Impedanzanalysen zur Herzminutenvolumen-Bestimmung lässt der PhysioFlow Enduro®-Algorithmus die thorakale Impedanz unter Ruhebedingungen unberücksichtigt, da dieser durch die Platzierung der Elektroden sowie die Anatomie der Testperson beeinflusst werden kann. Nichtsdestoweniger wurde das PhysioFlow Enduro® gegenüber der Fick-Methode bei gesunden und kranken Individuen validiert *(70,71)*. Weiterhin zeigte die im Rahmen dieser Arbeit mit dem PhysioFlow Enduro® ermittelte Regressionsgerade eine Zunahme in $\dot{Q}$ von 5,6 $L \cdot min^{-1}$ bei einer Steigerung der $\dot{V}O_{2max}$ von 1 $L \cdot min^{-1}$. Diese Zahlen decken sich mit invasiven Untersuchungen und bestätigen die Validität des Systems *(66,72,73)*.

3 Konzeption, Durchführung und Ergebnisse der Studien

Übergeordnetes Ziel der Studien war es, das Ausmaß der belastungsinduzierten BV-Veränderungen während Ausdauer- und Kraftbelastungen zu quantifizieren und deren Bedeutung für die körperliche Leistungsfähigkeit zu evaluieren. In diesem Kontext wurde in den **Studien I** und **II** der Einfluss des Herz-Kreislauf-Systems unter besonderer Berücksichtigung des Blutvolumens auf die maximale Sauerstoffaufnahme und damit die Ausdauerleistungsfähigkeit bestimmt. Untersucht wurde dabei 1) der biologische Zusammenhang zwischen dem Blutvolumen und den kardialen Strukturen, 2) der Einfluss von Blutvolumen und kardialen Strukturen auf das Schlagvolumen als maßgebliche Determinante des Herzminutenvolumens und 3) der Einfluss der belastungsinduzierten Plasmavolumen-Veränderungen auf mögliche Veränderungen im Schlagvolumen und der Sauerstofftransportkapazität während inkrementeller, kardiopulmonaler Ausbelastungstests. Diese Zusammenhänge wurden sowohl bei heterogen trainierten Männern (**Studie I**) als auch bei Frauen (**Studie II**) untersucht.

Weiterhin stellt **Studie III** eine Sekundäranalyse der Daten aus **Studie II** dar, die das Ziel hatte, den Einfluss 1) des Blutvolumens auf die gemessenen Laktatkonzentrationen und 2) der Plasmavolumen-Veränderungen auf Laktatkonzentrationen und Laktattransportkapazität während dynamischer Muskelarbeit zu bestimmen.

Studie IV war hingegen die erste Untersuchung, die sich mit absoluten Plasmavolumen-Veränderungen während eines erschöpfenden Einsatz-Krafttrainings an der Beinpresse und unter zusätzlicher Berücksichtigung des Säure-Basen-Haushalts, der Pufferkapazität und der Ventilation befasste.

An den Studien nahmen ausschließlich herzgesunde Männer und Frauen teil, die im Vorfeld der Visiten mündlich und schriftlich über die Studieninhalte und die damit verbundenen Risiken aufgeklärt wurden. Alle Teilnehmer*innen unterzeichneten anschließend eine schriftliche Einverständniserklärung und wurden darüber informiert, dass sie jederzeit und ohne Angabe von Gründen von der Teilnahme zurücktreten konnten. Für die Studienprotokolle lag ein positives Votum seitens der Ethik-Kommission der Universität Bayreuth vor. Nachfolgend werden Konzeption, Durchführung und Ergebnisse der einzelnen Untersuchungen detailliert beschrieben.

3.1 Studie I - Effect of Exercise-Induced Reductions in Blood Volume on Cardiac Output and Oxygen Transport Capacity

Studie I untersuchte den Zusammenhang zwischen BV, kardialen Dimensionen und $\dot{V}O_{2max}$ bei heterogen trainierten Männern. Weiterhin sollte erstmals der Einfluss der belastungsinduzierten Veränderungen im BV auf die Sauerstofftransportkapazität und $\dot{Q}$ quantifiziert werden. Hierfür führten insgesamt 24 Männer zwei kardiopulmonale Ausbelastungstests auf einem Fahrradergometer durch. Beim ersten Test wurden zunächst die $\dot{V}O_{2max}$ und maximale mechanische Leistung (P_{max}) bestimmt. Der zweite Test beinhaltete die Bestimmung des Herzminutenvolumens mittels Inertgas-Rückatmung (Innocor®) in Ruhe, bei 60 % P_{max} und kurz vor P_{max} aus dem ersten Testlauf. Ebenfalls wurden für die spätere Berechnung der BV-Veränderung und des CaO_2 die [Hb] respektive kapilläre Sauerstoffsättigung (ScO_2) bestimmt. Im Vorfeld der Testungen wurde die Körperzusammensetzung mittels bioelektrischer Impedanz analysiert. Weiterhin erfolgte eine echokardiographische Bestimmung der kardialen Dimensionen. Die Hbmass und das BV wurden bei allen Teilnehmern anhand von Doppel-Bestimmungen an aufeinanderfolgenden Tagen ermittelt.

Es konnte gezeigt werden, dass das BV als Resultat der PV-Veränderung bis zur maximalen Leistung um 567 ± 187 mL (8 %) abnahm, was mit einer Zunahme der [Hb] um 1,3 ± 0,4 $g \cdot dL^{-1}$ einherging. Gleichzeitig nahm die kapilläre Sauerstoffsättigung um ca. 6 % ab. Dies führte insgesamt zu einem leichten Anstieg des CaO_2, der jedoch nicht signifikant war. Weiterhin wurde ein enger und signifikanter Zusammenhang zwischen dem BV unter Ruhebedingungen sowie dem Herzvolumen ($r = 0,68$; $p = 0.001$) respektive der $\dot{V}O_{2max}$ ($r = 0,76$; $p < 0.001$) beobachtet. Ein ebenso signifikanter Zusammenhang wurde zwischen dem BV (sowohl unter Ruhebedingungen als auch während maximaler Belastung) und dem maximalen Schlagvolumen gefunden. Anhand des Anstiegs der Regressionsgeraden wurde ermittelt, dass ein Unterschied im BV um 1 L mit einem Unterschied im maximalen SV um 25 mL und im $\dot{Q}$ um 3,5 $L \cdot min^{-1}$ assoziiert war.

Zu den entscheidenden Erkenntnissen dieser Studie zählen 1) die erstmalige absolute Quantifizierung der BV-Veränderungen während inkrementeller Belastung, 2) die daraus resultierende Berechnung der Abnahme in $\dot{Q}$ in Höhe 1,6 $L \cdot min^{-1}$, 3) die Tatsache, dass die herbeigeführte Hämokonzentration den arteriellen Sauerstoffgehalt während der Belastung konstant hielt und 4) dadurch die Sauerstofftransportkapazität des kardiopulmonalen Systems trotz des möglichen negativen Einflusses der BV-Veränderungen auf $\dot{Q}$ mehr als kompensiert werden kann.

Grundsätzlich bestätigte diese Untersuchung ebenfalls, den positiven Zusammenhang zwischen dem Ausmaß des maximalen SV und dem BV. Es blieb aber weiterhin offen, welcher Zusammenhang zwischen dem BV (und den kardialen Dimensionen) und dem konkreten Verlauf des SV über die Zeit während körperlicher Belastung existiert. Dies ist der geringen Anzahl an möglichen Messzeitpunkten unter Nutzung der Inertgas-Rückatmung geschuldet. Da zugleich bis dato nur sehr wenige Ergebnisse zum Verhalten der SV-Antwort bei Frauen vorlagen, wurden für **Studie II,** in der der kontinuierliche Verlauf des SV registriert wurde, ausschließlich weibliche Teilnehmerinnen rekrutiert.

3.2 Studie II - Cardiac Stroke Volume in Females and its Correlation to Blood Volume and Cardiac Dimensions

Studie II untersuchte explizit den zeitlichen Verlauf des SV während einer inkrementellen Belastung auf dem Fahrradergometer. Hierfür wurde eine portable, nicht-invasive Herzleistungs-Beurteilungstechnik mit Analyse des transthorakalen Impedanzsignals (PhysioFlow® Enduro) herangezogen. Weiterhin wurde auch hier der Einfluss der belastungsinduzierten Veränderungen im BV auf die Sauerstofftransportkapazität und $\dot{Q}$ quantifiziert. Hierfür führten insgesamt 26 heterogen trainierte Frauen einen kardiopulmonalen Ausbelastungstest auf dem Fahrradergometer durch. $\dot{Q}$ wurde dieses Mal kontinuierlich und nicht wie in der vorherigen Studie zu drei Messzeitpunkten bestimmt. Kapilläre Blutproben zur Bestimmung der [Hb] und der O_2-Sättigung wurden ebenfalls alle drei Minuten während der Belastung entnommen. Im Vorfeld der Testung wurde die Körperzusammensetzung mittels bioelektrischer Impedanz analysiert und die Herzdimensionen durch eine 2D-Echokardiographie bestimmt. Die Hbmass und das BV wurden bei allen Teilnehmerinnen anhand von Doppel-Bestimmungen an aufeinanderfolgenden Tagen ermittelt.

Diese Studie ist nach bestem Wissen bis heute die erste, die eine fortlaufende Bestimmung des SV unter zeitgleicher Berücksichtigung des BV durchführte. Dadurch konnte dem zu einem bestimmten Zeitpunkt gemessenen SV ein unter Berücksichtigung der Volumenveränderungen angepasstes BV zugeordnet werden. Weiterhin inkludierte diese Studie ebenso die Herzstrukturen unter Skalierung der Daten auf die Körperoberfläche.

Es konnte gezeigt werden, dass das BV bis zum Belastungsabbruch im Mittel um 280 mL (5,7 %) abnahm. Gleichzeitig stieg die [Hb] signifikant um 0,8 $g \cdot dL^{-1}$ an. Das SV bildete im Mittel kein Plateau, sondern stieg bis kurz vor Belastungsabbruch progressiv an. Grundsätzlich war die SV-Antwort jedoch von großer interindividueller Variabilität geprägt. Interessanterweise

war das SV während der höheren Belastungsintensitäten signifikant mit dem BV korreliert, nicht jedoch im unteren submaximalen Bereich (40 % der $\dot{V}O_{2max}$). Teilnehmerinnen mit den höchsten BV in Ruhe zeigten die geringsten Zunahmen im SV (ΔSV) bis 40 % der $\dot{V}O_{2max}$ ($r = -0{,}40$; $p = 0{,}05$), aber die höchsten Zunahmen im weiteren Verlauf (zwischen 40 % - 80 % $\dot{V}O_{2max}$, $r = 0{,}45$; $p = 0{,}05$) der Belastung. Die kardialen Strukturen (LVEDV, LVMM und LVEDD), skaliert auf die Körperoberfläche, waren zu allen Messzeitpunkten signifikant mit dem SV korreliert, nicht jedoch mit der Veränderung des SV zwischen Ruhe- und Belastungswerten (ΔSV). Die belastungsinduzierten BV-Veränderungen waren ebenfalls nicht mit dem ΔSV korreliert. Zudem war in dieser Studie ein Unterschied im BV um 1 L mit einem Unterschied im maximalen SV um 16 mL und im $\dot{Q}$ um 2,5 $L \cdot min^{-1}$ assoziiert.

Grundsätzlich bestätigt sich auch bei Frauen der signifikante Zusammenhang zwischen BV und SV, allerdings kann berichtet werden, dass diese Korrelation mit zunehmender Belastung stärker ausfällt. Weiterhin scheint es so, dass eine Zunahme im SV unter submaximalen Bedingungen umso geringer ausfällt, je größer das BV unter Ruhebedingungen ist. Im weiteren Belastungsverlauf ist dieser Zusammenhang allerdings negativ und nur diejenigen mit einem hohen BV sind in der Lage ihr SV weiter zu steigern. Der auch in dieser Studie gefundene, mögliche negative Einfluss der BV-Veränderungen auf die SV-Antwort wird durch die Hämokonzentration und den damit einhergehenden Anstieg der O_2-Transportkapazität vollständig kompensiert.

3.3 Studie III - Relationship between Blood Volume, Blood Lactate Quantity and Lactate Concentrations during Exercise

Die substantiellen BV-Veränderungen, die in den **Studien I** und **II** festgestellt wurden, bildeten die Rationale für die Konzeption von **Studie III**. Grundlage der Überlegung war, dass eine Änderung im Volumen eines Mediums, in diesem Fall des BV, jegliche im Vollblut gemessenen Konzentrationen von Metaboliten beeinflussen müssten. Bestätigt wird diese Annahme zumindest theoretisch durch die in den **Studien I** und **II** beobachtete signifikante Zunahme der [Hb]. Da die bei Ausbelastungstests erhobenen [La^-] eine hohe Wertigkeit in der sportmedizinischen Diagnostik besitzen, wurden die Daten aus **Studie II** einer Sekundäranalyse unterzogen. Ziel dieser Analyse war es, den Einfluss des BV und der BV-Veränderungen auf die gemessenen [La^-] zu bestimmen. Hierfür wurden ebenfalls die absolute systemische Laktatmenge (La^-) sowie die Laktattransportkapazität im Plasma und den Erythrozyten bestimmt.

Diese Analyse konnte aufzeigen, dass 1) zum Zeitpunkt der maximalen mechanischen Leistung die [La^-] signifikant mit der La^- korreliert war ($r = 0.84$; $p < 0{,}0001$), 2) eine signifikante,

negative Korrelation zwischen [La^-] und BV existiert ($r = -0{,}44$; $p < 0{,}05$) und 3) die BV-Veränderung die Laktattransportkapazität um ca. 11 % reduzierte.

Diese Studie zeigt erstmals auf, dass gemessene [La^-] während einer bis zur Erschöpfung durchgeführten Belastung sowohl von der La^- als auch dem BV als Verteilungsmedium beeinflusst werden. Weiterhin war mit den BV-Veränderungen auch ein möglicher negativer Effekt auf den Laktattransport assoziiert.

3.4 Studie IV - Plasma Volume Shifts and Acid-Base Balance after a Single Bout of Resistance Exercise

Wie bereits erwähnt, haben sich die **Studien I** und **II** mit den BV-Veränderungen während inkrementeller, kardiopulmonaler Ausbelastungstests befasst. Im Bereich des Krafttrainings liegen bisher jedoch nahezu keine Daten vor, die sich mit der Rolle des BV und den belastungsinduzierten Volumenverschiebungen befasst haben. **Studie IV** hatte deshalb das Ziel, erstmals die absolute Veränderung des BV während eines bis zur Erschöpfung durchgeführten Einsatz-Krafttrainings zu quantifizieren. Zugleich war es das Ziel, Veränderungen im Sauerstofftransport, Säure-Base-Haushalt und der Ventilation ($\dot{V}E$) zu detektieren, um das Verhalten dieser Größen im Nachbelastungsverlauf zu verstehen.

Hierfür wurden 27 gesunde und Krafttrainings-erfahrene Männer rekrutiert, die ein Einsatz-Krafttraining an einer horizontalen Beinpresse durchführten. Vor und bis zu 15 Minuten nach Belastungsabbruch wurden [Hb] und Hct sowie Kenngrößen des Säure-Base-Haushalts bestimmt (pH, [HCO_3^-], [La^-], pCO_2). Zusätzlich der Anteil der Bikarbonat- (β_{bi}) und Nicht-Bikarbonatpufferung (β_{nbi}) an der Gesamtpufferkapazität (β_{tot}) berechnet. Die $\dot{V}E$ sowie $\dot{V}O_2$ und $\dot{V}CO_2$ wurden fortlaufend mittels Spirometrie gemessen. Im Vorfeld der Testung wurde die Körperzusammensetzung mittels bioelektrischer Impedanzanalyse bestimmt. Die Hbmass und das BV wurden bei allen Teilnehmerinnen anhand von Doppel-Bestimmungen an aufeinanderfolgenden Tagen ermittelt.

Das Einsatz-Krafttraining führte zu einer signifikanten Abnahme des PV um 560 mL (14 %). Dabei lagen die individuellen PV-Veränderungen zwischen −123 und −1091 mL (−2.9 and −23.9 %). Ebenfalls konnte bei Belastungsabbruch eine moderate metabolische Azidose mit einem mittleren pH-Wert von 7,30 festgestellt werden. Der pCO_2 war zu diesem Zeitpunkt noch unverändert, lag aber bereits eine Minute nach Abbruch signifikant niedriger (39,4 ± 4.3 vs. 34,4 ± 4.2 mm Hg, $p<0.0001$), was auch noch 15 Minuten nach Belastungsabbruch der Fall

war. Der Anteil der β_{nbi} war während der Nachbelastungsphase auf einem konstanten und niedrigen Niveau, während die respiratorische Komponente der Pufferung bis 15 Minuten nach Abbruch stetig zunahm und bis zu 50 % der Gesamtpufferung betrug.

Diese Studie ist die erste, die absolute Veränderungen im Plasmavolumen während eines Krafttrainings bestimmt hat. Auch gab es bisher noch keine Daten, die Rückschlüsse auf das Verhalten der Pufferkapazität unter Berücksichtigung der Ventilation während einer solchen Belastung zuließen. Zu den wichtigsten Erkenntnissen zählen 1) die belastungsinduzierte Abnahme des PV um ca. 560 mL (14 %), 2) die im Nachbelastungsverlauf durch die Hämokonzentration bedingte signifikante Zunahme des CaO_2, 3) die Tatsache, dass der pCO_2 mit Belastungsabbruch zunächst unverändert war, jedoch im Anschluss durch die gesteigerte Ventilation rapide abfiel und 4) die Tatsache, dass der Anteil der Nicht-Bikarbonatpufferung mit fortschreitender Erholung konstant blieb, die respiratorische Komponente der Pufferung jedoch stetig zunahm.

4 Synopse

Allen vorliegenden Untersuchungen liegt die zentrale Rolle des BV unter besonderer Berücksichtigung der BV-Veränderungen während dynamischer Muskelarbeit zugrunde, die in unterschiedlichen Teilaspekten untersucht wurden. Zum einen wurde der Zusammenhang von BV und kardialen Dimensionen sowie deren Wechselwirkung in Bezug auf das Herzminutenvolumen und die maximale Sauerstoffaufnahme bei herzgesunden Männern und Frauen untersucht (**Studie I** und **II**). Dies inkludiert ebenfalls eine umfassende Analyse der SV-Antwort, die vor allem in **Studie II** durchgeführt wurde. Zum anderen wurde der Einfluss der belastungsbedingten BV-Veränderungen während inkrementeller Belastungstests sowie beim Krafttraining auf die Sauerstoff- bzw. Laktattransportkapazität untersucht (**Studien I**, **II**, **III** und **IV**). Zusätzlich untersuchte **Studie IV** das Verhalten des Säure-Base-Status beim Krafttraining und Berücksichtigung der ventilatorischen Kompensation in der Nachbelastungsphase.

Das BV und die kardialen Dimensionen in ihrem Einfluss auf das SV und die $\dot{V}O_{2max}$

In **Studie I** (Innocor®) betrug die Zunahme in $\dot{Q}$ circa 6,8 $L \cdot min^{-1}$ für jede Zunahme in der $\dot{V}O_{2max}$ um 1 $L \cdot min^{-1}$ ($\dot{Q} = 6{,}88x\dot{V}O_{2max} - 5748$). In **Studie II** (PhysioFlow Enduro®) betrug die Zunahme in $\dot{Q}$ circa 5,6 $L \cdot min^{-1}$ für jede Zunahme in der $\dot{V}O_{2max}$ um 1 $L \cdot min^{-1}$ ($\dot{Q} = 5{,}59x\dot{V}O_{2max} + 6{,}05$). Diese Zahlen sind unter Berücksichtigung des Geschlechts nahezu identisch mit denen invasiver Messungen und stehen zunächst für die Validität des Innocor® und PhysioFlow Enduro® bei der Bestimmung des Herzzeitvolumens während körperlicher Aktivität *(72)*. Auf Grundlage der Steigung der jeweiligen Regressionsgeraden wurde anschließend berechnet, in welchem quantitativen Zusammenhang die einzelnen kardiovaskulären Größen stehen.

Bei den Männern aus **Studie I** wurde festgestellt, dass ein Unterschied des BV um 1000 mL mit einem Unterschied im SV um 25 mL einhergeht. Bei den Frauen betrug der Unterschied im SV 16 mL. Ginge man nun von einer theoretischen Erhöhung des BV um 2 L aus, so wie es durch systematisches Ausdauertraining durchaus zu Stande kommt *(74)*, würde dies einer Zunahme um 34 % (Männer) und 26 % (Frauen) des in den Studien maximal erreichten SV (147 vs. 124 mL) gleichkommen. Da das SV die wichtigste Determinante für eine hohe maximale Sauerstoffaufnahme bildet, wurde der quantitative Einfluss auf diese Größe ebenfalls bestimmt. So wurde bei einem Unterschied des BV um 1000 mL ein Unterschied in der $\dot{V}O_{2max}$ um 294 $mL \cdot min^{-1}$ (Männer) und 625 $mL \cdot min^{-1}$ (Frauen) gefunden. Erklärbar wird der Geschlechterunterschied wahrscheinlich durch die bei den Frauen gefundene, signifikante Korrelation zwischen $\dot{V}O_{2max}$ und $avDO_{2max}$. Dieser Zusammenhang war bei den Männern nicht signifikant.

Eine weitere mögliche Erklärung könnte aber auch in den deutlich höheren Werten für $\dot{Q}$ liegen, die bei den Männern gefunden wurden. Diese stehen im Zusammenhang mit einer kürzeren pulmonalen Transitzeit, die mit einer Entsättigung des Blutes einhergeht, was sich negativ auf die $\dot{V}O_{2max}$ auswirkt *(75)*.

Dass das BV die zentrale Einflussgröße auf das SV bildet, wurde bereits in mehreren experimentellen Untersuchungen dargestellt *(76,77)*. Dabei bildet ein höherer venöser Rückstrom, der durch ein höheres BV bedingt ist, die Grundlage für eine Zunahme des enddiastolischen Volumens und somit des SV. Dieser Zusammenhang konnte sowohl für heterogen trainierte Männer (**Studie I**) als auch Frauen (**Studie II**) bestätigt werden und deckt sich mit den Erkenntnissen aus der Literatur *(78)*. Dies galt dabei nicht nur für den signifikanten Zusammenhang zwischen dem SV (respektive $\dot{Q}$) und dem BV unter Ruhebedingungen, sondern auch für die Werte bei maximaler Leistung. Weiterhin blieben diese Resultate auch nach einer Skalierung der Daten auf die Körper- und Skelettmuskelmasse (**Studie I**) bzw. auf die Körperoberfläche (**Studie II**) signifikant, was den Einfluss unabhängiger Faktoren, zum Beispiel des Trainingsstatus, verdeutlicht.

Als das BV bei Untrainierten mittels Infusionen an das von Ausdauertrainierten angepasst wurde, stellt man fest, dass das SV bei den Untrainierten zwar zunahm, jedoch nicht an die maximalen Werte der Ausdauertrainierten heranreichte *(79)*. Dies legt nahe, dass das BV allein nicht für die Steigerung des SV durch Ausdauertraining verantwortlich ist, sondern weitere Faktoren wie eine morphologische Anpassung des Myokards eine nicht zu vernachlässigende Rolle spielen. Es gibt bis heute allerdings nur sehr wenige Studien, die sich mit dem integralen Zusammenspiel von BV, kardialen Dimensionen und SV auseinandersetzen. In den **Studien I** und **II** wurde für beide Geschlechter jeweils ein signifikanter Zusammenhang zwischen Herzvolumen bzw. LVMM und LVEDD und dem BV sowie dem SV gefunden. Für das sog. Sportherz gilt es als akzeptiert, dass dieses sowohl durch eine Zunahme im LVEDD und der LVMM, als auch durch eine Volumenzunahme des linken Vorhofs charakterisiert ist *(80)*. Da die durch Ausdauersport bedingten hämodynamischen Veränderungen einen primären Stimulus für ein kardiales Remodelling darstellen, legen die in diesen Studien gefundenen Ergebnisse nahe, dass das BV einen zentralen Einfluss auf diese Anpassung haben könnte. Wie bereits erwähnt, existieren diese Zusammenhänge auch nach Skalierung der Daten, was für einen gekoppelten Adaptationsprozess als Resultat eines langfristigen Trainingsstimulus spricht.

Belastungsbedingte BV-Veränderungen

Im Rahmen aller Studien wurde jeweils eine signifikante Abnahme des BV während dynamischer Muskelarbeit detektiert. Bei den Männern in **Studie I** nahm das BV bis zum Ende des kardiopulmonalen Ausbelastungstests um ~570 mL ab, was 8 % des Gesamtvolumens ausmacht. Bei den Frauen in **Studie II** reduzierte sich das BV um 280 mL (6 %). Da in **Studie IV** zusätzlich der Hämatokrit bestimmt wurde, konnten die Volumenänderungen ausschließlich auf das PV beziffert werden. Dieses nahm um ~560 mL ab (14 %), was einer Reduktion des BV von ca. 9 % entspricht. Wenngleich die Volumenänderungen vor allem auf eine intrazelluläre Akkumulation von osmotisch wirksamen Substanzen, d.h. insbesondere Laktat, zurückgeführt werden, so konnte in den **Studien I**, **II** und **IV** kein Zusammenhang zwischen dem Ausmaß der Volumenveränderungen (ΔBV) und der [La^-] bei Belastungsabbruch festgestellt werden. Im Vergleich zu den Männern verzeichneten die Frauen dabei eine deutlich niedrigere BV-Veränderung, was wahrscheinlich auf eine geringere aktive Muskelmasse zurückzuführen ist *(81)*. Auch in anderen Studien, die prozentuale Volumenänderungen bestimmt haben, wurden für Männer jeweils höhere Werte präsentiert *(36,82)*.

Setzt man die in den **Studien I** und **II** gefundenen BV-Verschiebungen in den Kontext der eingangs gerechneten Regressionen, so führte die Abnahme des BV um 570 mL bei den Männern (280 mL bei den Frauen) zu einer Reduktion des maximalen SV und der $\dot{V}O_{2max}$ um 14,2 mL (4,5 mL) respektive 133 $mL \cdot min^{-1}$ (156 $mL \cdot min^{-1}$). Dies würde bei den Frauen einer Reduktion der relativen $\dot{V}O_{2max}$ um 0,55 $mL \cdot min^{-1} \cdot mL^{-1}$ BV gleichkommen (0,23 $mL \cdot min^{-1} \cdot mL^{-1}$ BV bei den Männern). Wenngleich die Daten aus der Querschnittserhebung nicht kausal interpretiert werden dürfen, so stimmen die Zahlen der Frauen nahezu exakt mit experimentellen Daten überein, die unmittelbar nach einer Blutspende in Bezug auf eine Minderung der $\dot{V}O_{2max}$ gefunden wurden *(83)*.

Die bisherigen Betrachtungen quantifizieren den Einfluss der BV-Verschiebungen in ihrem Einfluss auf $\dot{Q}$ und die $\dot{V}O_{2max}$, berücksichtigen jedoch noch nicht, dass es dadurch auch zu einem signifikanten Anstieg der [Hb] und damit theoretisch zu einer Erhöhung des arteriellen Sauerstoffgehalts kommen müsste. In den **Studien I** und **II** kam es während inkrementeller Belastung zu einem mittleren Anstieg der [Hb] um 1,3 (Männer) respektive 0,8 $g \cdot dL^{-1}$ (Frauen), während die kapilläre Sauerstoffsättigung um 6 respektive 4 % abnahm. Dies führte zu einem konstanten CaO_2 bei den Männern und zu einem leichten aber dennoch signifikanten Anstieg bei den Frauen. Dieser ist in erster Linie durch den weniger stark ausgeprägten Abfall der ScO_2

erklärt. Auch in **Studie IV** blieb der CaO_2 bei Belastungsabbruch konstant ([Hb]: +1,2 $g \cdot dL^{-1}$, ScO_2: −1,2 %).

In der Summe haben die BV-Verschiebungen also nicht nur einen negativen Einfluss auf die SV-Antwort, sondern führen über die Hämokonzentration auch zur Konstanthaltung des arteriellen Sauerstoffgehalts. Berechnet man nun die Sauerstofftransportkapazität des kardiopulmonalen Systems für die **Studien I** und **II** jeweils mit und ohne den Einfluss der BV-Verschiebungen, so beträgt diese 5376 $mL \cdot min^{-1}$ und 5208 $mL \cdot min^{-1}$ (Männer) respektive 4314 $mL \cdot min^{-1}$ und 4153 $mL \cdot min^{-1}$ (Frauen). Diese Daten zeigen eindrucksvoll, dass die BV-Veränderungen den Abfall der Sauerstoffsättigung und des Herzminutenvolumens durch die Hämokonzentration mehr als kompensieren. Wie bei akuten Höheneffekten ist die Hämokonzentration aufgrund von vorübergehenden Volumenverschiebungen demnach als physiologische Anpassung des Körpers zu interpretieren, um die Sauerstofftransportkapazität zu erhalten (oder sogar zu verbessern) ohne dabei die Leistung zu beeinträchtigen *(84)*. Dies scheint dabei sowohl für inkrementelle Belastungen als auch für ein Krafttraining zu gelten.

Der Verlauf des SV während inkrementeller Belastung

Der Verlauf der SV-Antwort während inkrementeller Belastung wird bis heute intensiv diskutiert *(21,22)*. Während man lange Zeit davon ausging, dass das SV ab einer submaximalen Intensität von ca. 40 % der $\dot{V}O_{2max}$ eine Plateaubildung aufzeigt, so haben neuere Untersuchungen nahegelegt, dass dies lediglich auf untrainierte Personen zutrifft. Ausdauertrainierte hingegen sollen in der Lage sein, ihr SV bis zum Erreichen der $\dot{V}O_{2max}$ respektive maximalen Leistung progressiv zu steigern. Für die Registrierung unterschiedlicher Verläufe werden dabei neben biologischen auch immer wieder methodische Faktoren verantwortlich gemacht.

Während bei den Männern in **Studie I** das SV bis zur submaximalen Leistung (60 % $\dot{V}O_{2max}$) um 60 % zunahm, blieb es im weiteren Verlauf bis zum Ende der Belastung im Mittel unverändert, was eine Plateaubildung im SV nahegelegt. Im Gegensatz dazu zeigte die SV-Antwort bei den Frauen aus **Studie II** eine progressive Steigerung bis 80 % der $\dot{V}O_{2max}$. In beiden Studien wurde dabei eine große inter-individuelle Variabilität detektiert, was der Heterogenität der Teilnehmer*innen in Bezug auf den Trainingsstatus geschuldet ist. Die Theorie der Plateaubildung geht auf Studien zurück, die lediglich zwei oder drei Messzeitpunkte inkludierten, wobei das SV in Ruhe bereits eingeschlossen ist. Dies lässt jedoch eine ganzheitliche Analyse der SV-Antwort während Belastung nicht zu. Vella & Robergs berichteten von mindestens vier typischen SV-Verläufen, die bei inkrementeller Belastung in Abhängigkeit von Alter, Geschlecht und Trainingszustand zu erwarten sind *(19)*: ein progressiver Anstieg, eine Plateaubildung mit

und ohne sekundären Anstieg sowie eine Plateaubildung mit einem Abfall kurz vor Belastungsbruch. Alle genannten Verläufe konnten in **Studie II** gefunden werden. Zudem beobachteten wir in dieser Studie weitere vier Teilnehmerinnen, die ihr SV bis 80 % der $\dot{V}O_{2max}$ steigern konnten, bevor es zu einem Abfall kam (siehe Abbildung 5 A), was einen möglichen fünften Verlauf darstellen könnte. Die unterschiedlichen Verläufe zeigen auch, dass die „Plateaubildung", die bei den Männern gefunden wurde, möglicherweise gar keine darstellt, was die Notwendigkeit von kontinuierlichen Messmethoden zur Bestimmung des SV während Belastung unabdingbar macht.

Ein progressiver Anstieg im SV bis zur maximalen Leistung wird allgemein nur Ausdauertrainierten Personen zugeschrieben. Eine unbeantwortete Frage bleibt jedoch die nach dem Vorkommen eines solchen Verlaufs bei untrainierten oder moderat trainierten Personen. Diese Personengruppe zeigt für gewöhnlich eine große Variabilität im SV-Verlauf, die wir auch für unsere Studien bestätigen konnten. Bei der Frage nach den zugrundeliegenden Mechanismen werden grundsätzlich das Ausmaß des BV sowie die kardialen Dimensionen aufgeführt. Wir fanden sowohl in **Studie I** als auch in **Studie II** einen signifikanten Zusammenhang zwischen dem maximalen SV und dem BV. Allerdings war das maximale SV in beiden Studien auch signifikant mit der LVMM und dem LVEDD korreliert, wobei dieser Zusammenhang in **Studie II** besonders deutlich war. Wir konnten außerdem zeigen, dass je kleiner das BV unter Ruhebedingungen war, desto größer war die Zunahme im SV bis 40 % der $\dot{V}O_{2max}$ ($\Delta SV_{R\text{-}40\%}$ vs. BV_{rest}, $r = -0.40$, $p = 0.05$). Dies wird auch durch die großen inter-individuellen Unterschiede in der Zunahme des SV zwischen Ruhe- und submaximalen Werten ($\Delta SV_{R\text{-}40\%}$, 8-98 mL) zum Ausdruck gebracht. Niedrigere Blutvolumina müssten demnach zuerst zu einem Anstieg des zentralen BV führen, wodurch wiederum das SV ansteigen würde. Im weiteren Belastungsverlauf dreht sich diese Korrelation jedoch, wonach eine weitere Steigerung im SV nur mit höheren BV möglich ist ($\Delta SV_{40\text{-}80\%}$ vs. $BV_{40\%}$, $r = 0.45$, $p < 0.05$).

Das SV in Ruhe und bei maximaler Belastung war ebenfalls signifikant mit dem LVMM und LVEDD korreliert. Dieser Zusammenhang blieb auch nach Skalierung der Daten auf die Körperoberfläche bestehen, was die grundsätzliche Annahme, dass höhere SV auch mit größeren kardialen Dimensionen einhergehen, bestätigt. Allerdings wurde kein signifikanter Zusammenhang zwischen dem ΔSV und dem Ausmaß der kardialen Dimensionen gefunden. Daraus lässt sich schließen, dass die alleinige Berücksichtigung der kardialen Strukturen die Variation im SV nicht erklären kann und dass zusätzliche Faktoren, z. B. die kardiale Compliance oder die linksventrikuläre Kontraktilität das Verhalten des SV während einer dynamischen Belastung beeinflussen *(85)*. Allgemein deuten unsere Ergebnisse darauf hin, dass in erster Linie der

Frank-Starling-Mechanismus und wahrscheinlich auch die linksventrikuläre Funktion einen wesentlichen Einfluss auf die SV-Antwort während einer inkrementellen Belastung ausüben.

Blut- und Plasmavolumen während des Krafttrainings

Die in **Studie IV** (560 mL) gefunden maximalen Volumenverschiebungen sind deckungsgleich mit denen aus **Studie I** (570 mL). Hierbei muss jedoch konstatiert werden, dass die in **Studie I** präsentierten Werte direkt bei Belastungsabbruch berechnet wurden, während die Werte aus **Studie IV** aus der dritten Minute der Nachbelastungsphase stammen. Bei Belastungsabbruch betrugen die PV-Verschiebungen hingegen 472 mL. Diese Divergenz ist sehr wahrscheinlich durch die unterschiedliche absolute Belastungsdauer zwischen den Studien erklärt. Beim Krafttraining dauerte der absolvierte Satz im Mittel knapp über zwei Minuten, während die Teilnehmer beim kardiopulmonalen Belastungstest im Mittel über ca. 15 Minuten beansprucht wurden. Diese zeitliche Diskrepanz wird auch durch die bei Belastungsabbruch gefunden [La^-] reflektiert (**Studie I:** 13,4 mmol·L^{-1}, **Studie IV:** 7,20 mmol·L^{-1}). Berücksichtigt man den Verlauf der [Hb] und [La^-] nach Belastungsabbruch in **Studie IV**, so ist anzunehmen, dass die Volumenverschiebungen in den **Studien I** und **II** in den Nachbelastungsphasen noch etwas deutlicher hätten ausfallen müssen. Da bei beiden Studien jeweils von einer objektiven muskulären bzw. kardiopulmonalen Ausbelastung auszugehen ist, veranschaulichen diese Ergebnisse, dass das Ausmaß von BV-Verschiebungen nicht so sehr mit der Art der Belastung, sondern mit der Belastungsdauer sowie der dabei erreichten [La^-] zusammenhängt.

Diese Annahme wird ebenfalls durch eine Studie von Craig et al. bestätigt, in der prozentuale PV-Veränderungen während eines Krafttrainings berechnet wurden *(38)*. Hierbei fand man heraus, dass ein Krafttraining mit höheren Wiederholungszahlen (10-Wiederholungsmaximum) zu größeren PV-Verschiebungen führt, als ein Krafttraining mit niedrigeren Wiederholungszahlen (5-Wiederholungsmaximum). Gleichzeitig führte das Krafttraining mit den höheren Wiederholungszahlen auch zu höheren maximalen [La^-]. Da die höheren systemischen [La^-] gleichbedeutend mit höheren muskulären [La^-] sind, bedeutet dies eine höhere Konzentration osmotisch wirksamer Substanzen im intrazellulären Raum während des Protokolls mit dem 10-Wiederholungsmaximum. Dadurch wird mehr Flüssigkeit aus dem intravaskulären Raum in das aktive Muskelgewebe verschoben, was wiederrum die größere Abnahme des PV erklärt.

Säure-Base-Haushalt während des Krafttrainings

Obwohl das Interesse für ein erweitertes Verständnis der akuten und chronischen Effekte eines Krafttrainings steigt, sind viele physiologische Zusammenhänge und Mechanismen dieser Trainingsform bis heute unklar. In **Studie IV** wurde deshalb ebenfalls der Einfluss eines Einsatz-

Krafttrainings auf den Säure-Base-Haushalt und die Ventilation untersucht. Hierbei wurde zunächst festgestellt, dass bereits ein Satz eines erschöpfenden Beintrainings zu einer moderaten metabolischen Azidose mit einer signifikanten Abnahme des pH führt. Dies wurde bisher in erster Linie für ein Krafttraining mit mehreren Sätzen gezeigt *(86)*, während man bei einem Krafttraining an der Laktatschwelle keine pH-Änderung feststellen konnte *(87)*. Für eine Analyse der Regulation des pH-Werts und damit des metabolischen Profils während und nach einer körperlichen Belastung muss grundsätzlich auch die Ventilation berücksichtigt werden. Weiterhin erlaubt die Berechnung der einzelnen Anteile der Gesamtpufferkapazität auf Basis des pH und pCO_2 sowie der $[La^-]$ und $[HCO_3^-]$ weitere Rückschlüsse *(88)*, was bis heute jedoch für ein Krafttraining noch nicht durchgeführt wurde.

Bei Belastungsabbruch wurde anhand des Siggaard-Andersen-Nomogramms *(89,90)* eine moderate metabolische Azidose mit einem pH von 7,30 detektiert. Der pCO_2 war jedoch mit 39,7 mm Hg zum gleichen Zeitpunkt unverändert. Das Verhalten des pCO_2 beim Krafttraining unterscheidet sich grundsätzlich von dem, was während inkrementeller Belastung bekannt ist. Hier erfährt der pCO_2 für gewöhnlich einen Anstieg bis zur ersten ventilatorischen Schwelle und fällt danach mit zunehmender Belastung ab *(91)*. Der Abfall des pCO_2 wird dabei durch eine gesteigerte Ventilation ($\dot{V}E$) ausgelöst, wodurch vermehrt CO_2 abgeatmet wird. Wenngleich die $\dot{V}E$ bei Belastungsabbruch signifikant erhöht war, so lag sie dennoch deutlich unter den maximalen Werten, wie sie bei inkrementeller Belastung berichtet wurden und ist vielmehr vergleichbar mit Werten während eines Wingate-Tests *(92)*. Die Ursache für eine geringere maximale $\dot{V}E$ liegt beim Training in der Beinpresse in der durch das Trainingsgerät und die Bewegung eingeschränkten Atmung, die keine vollständige Belüftung der Lunge zulässt. Dies erschwert ebenfalls ein effizientes Abatmen von CO_2. Erst mit dem Wegfall dieser Restriktion erfährt der pCO_2 schließlich den erwartbaren Abfall, was durch einen signifikant niedrigeren Wert in der ersten Minute nach Belastungsabbruch (34,4 mm Hg) gekennzeichnet ist. Bereits an diesem Punkt lag dann nach dem Siggaard-Andersen-Nomogramm eine metabolische Azidose mit respiratorischer, wenngleich insuffizienter, Kompensation vor *(89,90)*. Dieser Blutstatus blieb bis 15 Minuten nach Ende der Belastung bestehen. Die niedrigsten mittleren pH-Werte wurden dabei nach fünf Minuten (7,24 ± 0,05) detektiert. Auch die $[HCO_3^-]$ und die Basenüberschüsse waren durch das Krafttraining signifikant reduziert und zeigten ebenfalls fünf Minuten nach Belastungsabbruch die niedrigsten Werte, was die Effizienz des offenen Kohlensäure-Bikarbonat-Puffersystems widerspiegelt.

Die $\dot{V}O_2$ war im Vergleich zum Ausgangswert bei Belastungsabbruch signifikant erhöht, was auf einen teilweise aeroben Stoffwechsel hindeutet. Allerdings scheint die $\dot{V}O_2$ während des

Krafttrainings auch durch die wiederholte Vasokonstriktion eingeschränkt zu sein *(93)*. Der Anstieg der $\dot{V}O_2$ nach dem Belastungsabbruch lässt sich wiederrum durch einen erhöhten aeroben Stoffwechsel, die Auffüllung der O_2-Speicher, d. h. des Myoglobins und insbesondere durch eine erhöhte Glykogenauffüllung erklären *(94)*. Außerdem ist die Oxyhämoglobin-Dissoziationskurve, die sich im p50 (O_2-Partialdruck des Blutes, bei dem 50 % Sättigung des Hämoglobins mit Sauerstoff vorliegt) widerspiegelt, infolge der metabolischen Azidose nach rechts verschoben, was als Bohr-Effekt bekannt ist *(95)*. Diese Rechtsverschiebung scheint jedoch nur in geringem Ausmaß einen negativen Effekt auf die arterielle O_2-Sättigung zu haben, da der Sauerstoffpartialdruck (pO_2) bereits eine Minute nach Belastungsabbruch sowie im weiteren Verlauf der Nachbelastungsphase aufgrund der erhöhten Ventilation ansteigt. Andererseits verbessert die Rechtsverschiebung der Oxyhämoglobin-Dissoziationskurve auch die O_2-Versorgung innerhalb der Muskelzellen. Dieser Prozess wird dadurch noch optimiert, dass aufgrund des eingeschränkten Blutflusses während des Krafttrainings der pCO_2 im Muskelgewebe durch das freigesetzte Laktat massiv ansteigt, wodurch der pH-Wert weiter sinkt und das Kapillarblut nahezu entsättigt wird. Auf diese Weise ermöglichen die belastungsbedingten PV-Verschiebungen in Kombination mit der metabolische Azidose eine effektivere Sauerstoffversorgung der Arbeitsmuskulatur während und nach dem Krafttraining, was theoretisch auch wesentlich zur muskulären Erholung zwischen mehreren Arbeitssätzen beitragen sollte.

Auf Basis des pH, der $[HCO_3^-]$ und der $[La^-]$ wurden anschließend die Anteile der Bikarbonat- (β_{bi}) und Nicht-Bikarbonatpufferung (β_{nbi}) an der Gesamtpufferkapazität (β_{tot}) berechnet. Weiterhin konnte unter Berücksichtigung des pCO_2 ebenfalls die respiratorische bzw. nicht-respiratorische Komponente der β_{bi} berechnet werden. Diese Berechnungen wurden für ein Krafttraining bisher noch nicht durchgeführt und erlauben somit einen wertvollen Einblick in die Regulation der Puffersysteme im Anschluss an eine erschöpfende Belastung. Dabei konnte gezeigt werden, dass die β_{nbi} unmittelbar bei Belastungsabbruch, als eine respiratorische Kompensation noch nicht stattgefunden hat, erwartungsgemäß am höchsten war. Im weiteren Verlauf nahm sie dann bis drei Minuten nach Abbruch weiter ab und blieb anschließend auf einem konstant niedrigen Niveau. Im Gegensatz dazu nahm die respiratorische Komponente der β_{bi} im Laufe der Nachbelastungsphase kontinuierlich zu, was in einem Anteil von über 50 % an der Gesamtpufferung 15 Minuten nach Abbruch mündete. Während diese Daten erstmals für das Krafttraining präsentiert wurden, so sind sie vergleichbar mit den Zahlen von Böning et al., die die Gesamtpufferkapazität bei einer inkrementellen Fahrradergometrie berechnet haben. Dies trifft ebenso auf den zeitlichen Verlauf der Puffergrößen in der Nachbelastungsphase zu

(88). Allerdings ist im Gegensatz zu der bei Böning et al. gewählten Belastung kein respiratorischer Anteil der β_{bi} bei Belastungsabbruch festgestellt worden, was sich möglicherweise durch die bereits erwähnte Restriktion der Atmung beim Krafttraining erklären lässt.

Aus sportpraktischer Sicht sind diese Erkenntnisse vor allem für ein Mehrsatz-Krafttraining relevant. Hier geht man davon aus, dass es im Trainingsverlauf zu einer Akkumulation von [La^-] und Wasserstoffprotonen und somit einer zunehmenden metabolischen Azidose kommt. Dies ist allgemein mit einer fortschreitenden Ermüdung und einem Leistungsabfall in den Folgesätzen verknüpft ist *(96)*. Im Krafttraining liegt die Pausendauer in Abhängigkeit von Intensität und Umfang für gewöhnlich zwischen zwei und fünf Minuten *(97)*. Eine metabolische Azidose lag in **Studie IV** jedoch nicht nur unmittelbar nach dem Arbeitssatz, sondern auch noch 15 Minuten danach vor, was für einen Akkumulationseffekt bei den oben genannten Pausendauern sprechen würde. Da eine Verlängerung der Pausendauer die Gesamttrainingsdauer erheblich verlängern würde, könnte stattdessen die anschließende Durchführung einer Trainingsübung für nicht-belastete, kleinere Muskelgruppen eine Möglichkeit sein, um die metabolische Azidose zu entkräften und Leistungseinbußen im Folgesatz zu vermeiden.

Schlussfolgerung

Das BV stellt die zentrale Größe des kardiopulmonalen Systems in Bezug auf die Leistungsfähigkeit dar. Dabei ist ein hohes BV die wichtigste Voraussetzung für das Erreichen eines hohen maximalen SV und somit einer hohen $\dot{V}O_{2max}$ während inkrementeller Belastung. Die SV-Antwort unterliegt sowohl bei Männern als auch bei Frauen grundsätzlich großen inter-individuellen Schwankungen und lässt sich nur durch eine kontinuierliche Herzminutenvolumen-Bestimmung ganzheitlich analysieren. Dadurch konnte auch erstmals gezeigt werden, dass Individuen mit einem hohen BV zunächst nur geringe Anstiege im SV während submaximaler Intensitäten erfahren, im Anschluss allerdings in der Lage sind, dieses bis zur maximalen Belastung weiter zu steigern. Ebenfalls wurde gezeigt, dass das SV mit den kardialen Dimensionen korreliert, insbesondere der linksventrikulären Muskelmasse und dem linksventrikulären enddiastolischen Durchmesser. Für einen progressiven Verlauf der SV-Antwort während inkrementeller Belastung scheint aber in erster Linie die Höhe des BV über die Generierung eines hohen venösen Rückstroms verantwortlich zu sein. Es kann aber davon ausgegangen werden, dass die durch ein höheres BV bedingten hämodynamischen Veränderungen den primären Stimulus für ein kardiales Remodelling darstellen. Somit ist das BV nicht nur die wichtigste Determinante des

SV, sondern hat wahrscheinlich auch einen zentralen Einfluss auf trainings-induzierte myokardiale Anpassungen.

Zusätzlich wurde auf Basis der Regressionsberechnungen erstmals der Zusammenhang zwischen den einzelnen kardiopulmonalen Größen quantifiziert. So ist ein Unterschied im BV um 1000 mL bei Männern und Frauen mit einem Unterschied im SV um 25 mL respektive 16 mL assoziiert. Derselbe Unterschied im BV führt wiederrum zu einem Unterschied im Herzminutenvolumen von 3.5 $L \cdot min^{-1}$ respektive 2.5 $L \cdot min^{-1}$, sowie in der $\dot{V}O_{2max}$ von 294 $mL \cdot min^{-1}$ und 625 $mL \cdot min^{-1}$.

Das BV unterliegt während dynamischer Muskelarbeit hohen Schwankungen, die sich in substantiellen PV-Verschiebungen äußern. Diese fallen für Männer grundsätzlich höher aus als für Frauen und sind in ihrem Ausmaß abhängig von der Belastungsdauer und der dabei erreichten metabolischen Stoffwechsellage. Die PV-Verschiebungen führen bei beiden Geschlechtern und sowohl bei Ausdauer- als auch Kraftbelastungen durch einen Anstieg der [Hb] zu einem stabilen CaO_2. Ebenso konnte gezeigt werden, dass die Laktattransportkapazität durch die BV-Verschiebungen negativ beeinflusst wird und dass die $[La^-]$ während maximaler muskulärer Belastung sowohl von der systemischen Laktatmenge als auch dem BV anhängig sind. Dabei ist ein höheres BV grundsätzlich mit niedrigeren $[La^-]$ verknüpft. Zusammenfassend verdeutlichen diese Ergebnisse den umfangreichen Einfluss des BV auf strukturelle und funktionelle Parameter.

Für das Krafttraining existierte zudem bisher keine Studie, die sich mit der integrativen Antwort von PV-Verschiebungen, Säure-Base-Haushalt und Ventilation beschäftigt hat. Es konnte erstmals gezeigt werden, dass die infolge eines Beintrainings gefundene moderate metabolische Azidose bei Belastungsabbruch nicht respiratorisch kompensiert wird, was möglicherweise durch die mit dem Krafttraining assoziierte Restriktion der Atmung erklärt werden kann. Dafür steigt in der Nachbelastungsphase der berechnete Anteil der respiratorischen Kompensation an der Gesamtpufferkapaziät stetig an, wobei auch 15 Minuten nach Beendigung der Belastung noch keine vollständige Regeneration in Bezug auf den Säure-Basen-Haushalt vorlag. Weiterhin ermöglichen die belastungsbedingten PV-Verschiebungen in Kombination mit der metabolische Azidose eine effektivere Sauerstoffversorgung der Arbeitsmuskulatur während und nach dem Krafttraining. Diese Ergebnisse verdeutlichen die Wechselwirkung von Blut, Atmung und Puffersystemen während körperlicher Belastung und erlauben somit eine ganzheitliche Analyse system-physiologischer Prozesse.

5 Eigenanteil an den einzelnen Studien und Publikationen

Studie I | **Effect of Exercise-Induced Reductions in Blood Volume on Cardiac Output and Oxygen Transport Capacity**

Die Studien I und II waren Teil des Projekts „Leistungslimitierung durch das Herz-Kreislauf-System im Ausdauersport“. Für diese Studien habe ich in Absprache mit Prof. Dr. Walter Schmidt ein in Grundzügen bereits bestehendes Studiendesign weiterentwickelt. In Studie I ergänzte ich das Konzept durch eine Modifizierung der Probandenauswahl und der Berücksichtigung weiterer Messparameter. Im Zuge dessen habe ich alle praktischen Arbeiten im Labor selbstständig durchgeführt. Ich habe im Anschluss die Ergebnisse statistisch ausgewertet und das Manuskript angefertigt. Abschließend habe ich die Empfehlungen der externen Gutachter in das Manuskript eingearbeitet.

Studie II | **Cardiac Stroke Volume in Females and its Correlation to Blood Volume and Cardiac Dimensions**

Studie II wurde in Absprache mit Prof. Schmidt eigenständig konzipiert. Auch bei dieser Studie führte ich den Großteil der praktischen Laborarbeiten eigenständig durch. Unterstützt wurde ich hierbei von Sandra Ficher, die im Rahmen der Untersuchung ihre Abschlussarbeit anfertigte. Ich habe im Anschluss die Ergebnisse statistisch ausgewertet und das Manuskript angefertigt. Abschließend habe ich die Empfehlungen der externen Gutachter in das Manuskript eingearbeitet.

Studie III | **Relationship between Blood Volume, Blood Lactate Quantity and Lactate Concentrations during Exercise**

Bei dieser Untersuchung handelt es sich eine Sekundäranalyse von Studie II. Auch hier habe ich die Ergebnisse statistisch ausgewertet und das Manuskripts erstellt. Im Anschluss habe ich die Revision der externen Gutachter in das Manuskript eingearbeitet.

Studie IV | **Plasma Volume Shifts and Acid-Base Balance after a Single Bout of Resistance Exercise**

Auch hier habe ich in Absprache mit Prof. Dr. Schmidt das Studiendesign erarbeitet. Anschließend habe ich alle praktischen Laborarbeiten eigenständig durchgeführt. Während der Visiten

im Kraftraum wurde ich von Frau Rebecca Zimmer unterstützt, die einen Teil der Messungen in ihre Abschlussarbeit einfließen ließ. Ich habe im Anschluss die Ergebnisse statistisch ausgewertet, das Manuskript angefertigt und dieses beim *Scandinavian Journal of Medicine & Science in Sports* eingereicht. Nach Begutachtung werde ich mögliche Empfehlungen der externen Gutachter in das Manuskript einarbeiten.

6 Artikel I: Effect of Exercise-Induced Reductions in Blood Volume on Cardiac Output and Oxygen Transport Capacity

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Abstract

We wanted to demonstrate the relationship between blood volume, cardiac size, cardiac output and maximum oxygen uptake ($\dot{V}O_{2max}$) and to quantify blood volume shifts during exercise and their impact on oxygen transport. Twenty-four healthy, non-smoking, heterogeneously trained male participants (27 ± 4.6 years) performed incremental cycle ergometer tests to determine $\dot{V}O_{2max}$ and changes in blood volume and cardiac output. Cardiac output was determined by an inert gas rebreathing procedure. Heart dimensions were determined by 3D echocardiography. Blood volume and hemoglobin mass were determined by using the optimized CO-rebreathing method. The $\dot{V}O_{2max}$ ranged between 47.5 and 74.1 $mL \cdot min^{-1} \cdot kg^{-1}$. Heart volume ranged between 7.7 and 17.9 $mL \cdot kg^{-1}$ and maximum cardiac output ranged between 252 and 434 $mL \cdot min^{-1} \cdot kg^{-1}$. The mean blood volume decreased by 8 % (567 ± 187 mL, $p = 0.001$) until maximum exercise, leading to an increase in [Hb] by 1.3 ± 0.4 $g \cdot dL^{-1}$ while peripheral oxygen saturation decreased by 6.1 ± 2.4 %. There were close correlations between resting blood volume and heart volume ($r = 0.73$, $p = 0.002$), maximum blood volume and maximum cardiac output ($r = 0.68$, $p = 0.001$), and maximum cardiac output and $\dot{V}O_{2max}$ ($r = 0.76$, $p < 0.001$). An increase in maximum blood volume by 1.000 mL was associated with an increase in maximum stroke volume by 25 mL and in maximum cardiac output by 3.5 $L \cdot min^{-1}$. In conclusion, blood volume markedly decreased until maximal exhaustion, potentially affecting the stroke volume response during exercise. Simultaneously, hemoconcentrations maintained the arterial oxygen content and compensated for the potential loss in maximum cardiac output. Therefore, a large blood volume at rest is an important factor for achieving a high cardiac output during exercise and blood volume shifts compensate for the decrease in peripheral oxygen saturation, thereby maintaining a high arteriovenous oxygen difference.

Keywords: stroke volume, heart volume, hemoglobin concentration, peripheral oxygen saturation, arterial oxygen content

Introduction

Over the years, it has been well established that cardiac output ($\dot{Q}$) is a major limiting factor for the maximum oxygen uptake ($\dot{V}O_{2max}$) during exercise *(4,5,98)*. $\dot{Q}$ equals the product of heart rate (HR) and stroke volume (SV), and is largely determined by a harmonic structural and functional adaption of the heart, where especially cardiac compliance is a prerequisite for large end-diastolic volumes *(99,100)*. If these prerequisites are given, the heart, e.g. the athletic heart – which is characterized by greater dimensions, specifically harmonically increased left-ventricular dimensions *(101,102)* – has a greater ability to use the Frank-Starling-mechanism. This well described mechanism allows for an efficient realization of SV due to a preload mediated stretch of the myocardium *(103)*. The preload largely depends on the circulating blood volume (BV), which therefore plays a key role for cardiac function. Unsurprisingly, previous studies revealed a strong positive relationship between BV and $\dot{V}O_{2max}$, which is mainly attributable to an increased venous filling resulting in a larger $\dot{Q}_{max}$ *(80)*. This effect has been demonstrated in cross-sectional *(104,105)* and longitudinal, i.e., manipulative studies *(20,76,106)*.

Noteworthy, BV has been shown to decrease during incremental exercise to exhaustion, due to a reduction in plasma volume by approx. 10 %, however, SV was not measured *(36)*. Consequently, this exercise mediated BV reduction might impair venous return during moderate and intensive exercise and exert a limiting effect on SV and, according to the Fick principle, $\dot{V}O_{2max}$. On the other hand, the concomitant increase in hemoglobin concentration [Hb] factually augments O_2 transport capacity. This would allow to mitigate the exercise induced arterial O_2 desaturation *(75,107)* and thereby enabling a sufficient arterio-venous oxygen difference during exercise at high intensities. Moreover, there seems to be an interaction between $\dot{Q}_{max}$ and the arterial oxygen content (CaO_2), as recent studies have demonstrated a regulatory effect of the CaO_2 on the $\dot{Q}$ response during dynamic exercise *(108,109)*.

Interestingly, percentage changes in BV during exercise have been evaluated before *(110)*, but data on absolute changes are scarce. Therefore, the effects of temporary BV changes during exercise on oxygen transport and endurance performance have not yet been fully elucidated. The first aim of this study was to quantify absolute BV changes during moderate and maximal exercise and to calculate their possible influence on SV, $\dot{Q}$, and $\dot{V}O_2$, while evaluating structural cardiac variables. Second, we wanted to quantify the scale of changes in CaO_2 due to the combined effects of hemoconcentration and exercise-induced oxygen desaturation. Using these data, we aimed to calculate whether the potentially beneficial effects of hemoconcentration for

oxygen transport might compensate or even exceed the detrimental effects of a diminished BV on the SV and the decreasing arterial oxygen desaturation during exercise.

Methods

Participants

Twenty-four healthy, nonsmoking and very heterogeneously trained males were included in the study (see Tab. 1 for subject characteristics). We explicitly focused on selecting participants with a wide range of performance status to compare the expected different structural and functional properties. The participants provided written consent after they were informed about the content of the study, the associated risks and the possibility to withdraw without indication of any reason. The study was approved by the ethics committee of the University of Bayreuth in Germany.

Tabelle 1. Subject characteristics.

n=24	**Mean±SD**	**Min.**	**Max.**
Age (y)	27.0±4.6	20	43
Height (cm)	183.5±6.5	171	199
Body mass (kg)	77.8±8.5	67.4	106.6
BMI ($kg \cdot m^{-2}$)	23.1±1.7	19.6	26.9
Lean body mass (kg)	68.2±6.8	56.0	89.1
Fat mass (%)	12.3±3.8	5.2	21.9
Ferritin ($\mu g \cdot L^{-1}$)	129±53	41	240

The data are presented as the mean values ± standard deviations. Min=minimum, Max=maximum. BMI=body mass index.

Study design

Participants performed two cycle ergometer tests on consecutive days. During the first ergometer test, the maximum oxygen uptake ($\dot{V}O_{2max}$) was determined. The second test followed a similar protocol and was performed to measure SV and $\dot{Q}$ at 60 % and near 100 % of the first test's maximum power (P_{max}) using an inert gas rebreathing method. Simultaneously, hemoglobin concentration for the calculation of BV (see equation 2) and peripheral hemoglobin-O_2 saturation (SpO_2) were determined. Prior to the performance tests, anthropometric measurements including body composition were conducted using bioelectrical impedance analysis. A cubital

venous blood sample was drawn to determine basic hematological parameter and ferritin levels in order to exclude any iron deficiencies. The heart dimensions were determined by 3D echocardiography. BV and Hbmass were measured twice on consecutive days using the optimized CO-rebreathing method *(50,51)*. All measurements took place within 7 days and, except for the echocardiography, were carried out under standardized environmental conditions in our laboratory (room temperature: 21.5 °C, barometric pressure: ~736 mmHg).

Analytical procedures and echocardiography

Lean body mass and fat mass were measured twice consecutively using bioelectrical impedance analysis (InBody 720, InBody Co., Seoul, South Korea). Cubital venous blood samples (8 mL) were taken after the participants rested for 15 minutes in a seated position. Heparinized blood samples were analysed using a fully automated haematology system (Sysmex XN 1000-1-A, Sysmex, Norderstedt, Germany) for basic hematological parameters. In the serum, the ferritin concentration and C-reactive protein (CRP) level were determined by enzyme immunoassays [ferritin: LKFE1, ELISA & Immulite 1000 (Siemens Healthcare Diagnostics GmbH, Germany); CRP: highly sensitive – LKCRP1, ELISA & Immulite 1000 (Siemens Healthcare Diagnostics GmbH, Germany)]. Transthoracic echocardiography was conducted using a commercially available cardiology ultrasound system (Philips EPIC 7, Phillips Medical Systems, Andover, MA, USA) with a 1.0-5.0 MHz sector array transducer (Philips S5-1, Phillips Medical Systems, Andover, MA, USA) to measure both the end-systolic and end-diastolic volumes, left ventricular muscle mass (LVMM), left ventricular end-diastolic diameter (LVEDD) and SV at rest. Heart volume (HV) was determined according to the methods described by Dickhuth and colleagues *(111)*.

Incremental ergometer tests

Aerobic performance was determined using an incremental protocol on a cycle ergometer (Excalibur, Lode, Groningen, Netherlands). After a 3-minute warm-up phase of 100 Watts, the mechanical power output was continuously increased by 50 Watts every 3 minutes (stepwise by 17, 17 and 16 Watts per minute) until subjective exhaustion was reached. $\dot{V}O2$ was determined via breath-by-breath technology (Innocor system, Innovision, Glamsbjerg, Denmark) and calculated as the mean value across the last 30 seconds before exhaustion. Capillary blood samples were taken from a hyperemized earlobe to quantify the lactic acid concentrations before exercise, every 3 minutes during exercise, immediately at exhaustion and 1, 3, 5 and 7 minutes after exhaustion (Biosen S-Line, EKF-Diagnostic, Barleben, Germany). During the second test, capillary blood samples were taken for the measurement of [Hb] (HemoCue 201,

HemoCue AB, Ängelholm, Sweden) at 60 % and near 100 % of the first test's Pmax to calculate changes in BV during the exercise period. Peripheral oxygen saturation (SpO2) was continuously determined by finger pulse oximetry (9590 Oximeter, Nonin Medical Inc., Plymouth, U.S.A.) and arterial oxygen content (CaO_2) was calculated according to formula 1:

$$CaO_2\ (mL \cdot \mathrm{dL}^{-1}) = [Hb]\ (g \cdot \mathrm{dL}^{-1}) \times SpO_2\ (\%) \div 100 \times 1.39 \quad (1)$$

Measurement of cardiac output, stroke volume and arteriovenous oxygen difference during exercise

SV, $\dot{Q}$ and $avDO_2$ were determined by inhaling a mixture of oxygen and two inert gases, i.e., nitrogen oxide (N_2O, 0.5 %) and sulphur hexafluoride (SF_6, 0.1 %) with a photoacoustic gas analyser (Innocor system, Innovision, Glamsbjerg, Denmark). Because this rebreathing manoeuvre might impair test performance, two tests were performed: one for the determination of $\dot{V}O_{2max}$ and one for the determination of $\dot{Q}$. The starting points for the rebreathing measurements during the second test were at 60 % P_{max} and the last fully completed 1-minute increment from the first ergometer test, respectively. Both rebreathing procedures took place after 10 seconds in the respective stages. Each rebreathing process lasted approximately 10 seconds and consisted of five respiratory cycles. $\dot{Q}$ was then derived from the changes in the concentrations of the inert gases in the expiratory volumes. SV was calculated on the basis of $\dot{Q}$ and heart rate (HR), and $avDO_2$ was calculated by applying the Fick equation. The typical error of this method in our lab was 4.9 % at 200 Watts, which is in line with earlier research *(112)*.

Determination of hemoglobin mass and total blood volume

At least 2 hours after the incremental test, when the plasma volumes had returned to pre-exercise values *(113)*, Hbmass, total blood (BV), plasma (PV) and erythrocyte (RCV) volumes were determined using the optimized CO-rebreathing method according to the methods reported by *(50,51,114)*. In brief, an individual dose of carbon monoxide (CO; 0.8–1.0 $mL \cdot kg^{-1}$) was administered and rebreathed along with 3 L of pure oxygen for 2 minutes. Capillary blood samples were taken before and 6 and 8 minutes post-administration of the CO dose. The blood samples were analysed for the determination of %HbCO using an OSM III hemoximeter (Radiometer, Copenhagen, Denmark). Hbmass was calculated on the basis of the mean change in %HbCO before and after CO was rebreathed. BV was then calculated according to formula 2:

$$BV\ (mL) = Hbmass\ (g) \times 100 \div [Hb]\ (g \cdot \mathrm{dL}^{-1}) \times F^{-1} \quad (2)$$

where $[Hb]_{ven}$ = venous hemoglobin concentration and F = cell factor at sea level *(52)*. For the calculations of BV during exercise, capillary [Hb] was measured during the second cycle ergometer test and modified for the venous conditions *(115)*. Since the Hbmass does not change over short periods of time *(56)*, the temporally offset determination of the [Hb] for the calculation of the BV is possible without compromising accuracy. For a detailed description and the accuracy of the methods see *(50,51,114)*. In our laboratory, the typical error for Hbmass is 1.5 %, which is comparable to previous investigations *(116,117)*, while the typical error for BV is 2.5 %.

Statistical analysis

The data are presented as the arithmetic means and standard deviations. Statistical analysis was conducted using IBM SPSS Statistics 26 (IBM, Armonk, U.S.A.). A one-way ANOVA with repeated measures followed by post-hoc tests with Bonferroni correction were performed to find significant differences between the resting, submaximal exercise and maximal exercise conditions. Simple linear regression and correlation analysis was performed to assess the relationships between two variables. The level of significance was set to $p \leq 0.05$ (*).

Results

As a result of the intended heterogeneity of the participants, absolute and relative performance as well as hematological and cardiac characteristics showed large interindividual variability (Tab. 2). Relative values for $\dot{V}O_{2max}$ ranged between 47.5 and 74.1 $mL \cdot min^{-1} \cdot kg^{-1}$. BV and Hbmass ranged between 75 and 101 $mL \cdot kg^{-1}$ and 10.6 and 14.2 $g \cdot kg^{-1}$, respectively. HV ranged between 7.7 and 17.9 $mL \cdot kg^{-1}$. Left ventricular end diastolic diameter (LVEDD) and muscle mass (LVMM) ranged between 45 and 63 mm and 116 and 303 g, respectively.

Tabelle 2. Performance and cardiological data and hemoglobin mass.

	Mean ± SD	**Min.**	**Max.**
P_{max} (W)	377±48	267	450
$\dot{V}O_{2max}$ (mL·min^{-1})	4624±484	3481	5520
$\dot{V}O_{2max}$ (mL·min^{-1}·kg^{-1})	59.8±6.6	47.5	74.1
RER_{max}	1.2±0.1	1.1	1.4
$[La^-]_{max}$ (mmol·L^{-1})	13.5±2.4	9.2	17.2
Hbmass (g)	980±124	746	1365
Hbmass (g·kg^{-1})	12.6±.1.1	10.6	14.2
ESV (mL)	77.9±21.4	31	119
EDV (mL)	172.9±34.1	86	249
HV (mL)	1101±213	560	1575
HV (mL·kg^{-1})	14.2±2.2	7.7	17.9
LVEDD (mm)	52.4±4.6	45	63
LVMM (g)	184±49	115	303

The data are presented as the means±standard deviations. Min.=Minimum, Max.=Maximum, P=Power, $\dot{V}O_{2max}$= maximum oxygen uptake, RER_{max}=maximum respiratory exchange ratio, $[La^-]_{max}$=maximum lactate concentration, Hbmass=hemoglobin mass, ESV=endsystolic volume, EDV=enddiastolic volume, HV=heart volume, LVEDD=left ventricular enddiastolic diameter, LVMM=left ventricular muscle mass.

Exercise study

BV decreased until maximum exercise by 8 % (556±187 mL, p<0.001, Fig. 3). There was a moderate correlation between the BV at rest (BV_{rest}) and the amount of intravasal fluid lost until maximum exercise (r=0.47, p=0.04); however, when percentage changes were calculated, no such relationship exists. Mean SV significantly increased from resting to submaximal exercise by 54±20 mL (p<0.001) with no significant difference in the further course until maximum exercise. However, large variability in the SV response was detected, especially from submaximal to maximal exercise with athletes demonstrating a progressive increase, plateau formation or a drop in SV. There was no correlation between the SV response from submaximal to maximal conditions and relative VO_{2max}, BV_{max} and the amount of BV shifted in the same time interval. HR continuously increased until maximal exercise, as did submaximal and maximal $avDO_2$ and $\dot{Q}$ (Tab. 3). [Hb] significantly increased until maximum exercise by 8.5 % (1.3±0.4 g·dL^{-1}, p<0.001), while the SpO_2 level in the capillary blood decreased by approximately 6.1 % (p=0.001, Tab. 3). Arterial oxygen content (CaO_2) remained unchanged between resting, submaximal and maximal exercise conditions (Tab. 3).

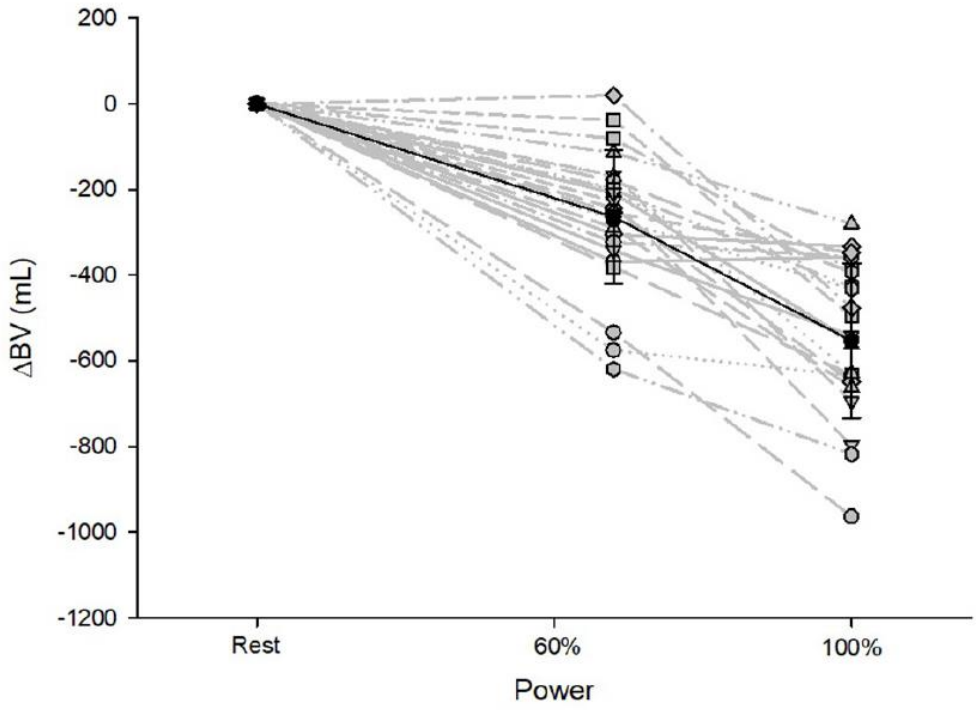

Abbildung 3. Changes in BV from resting to submaximal (60 % P_{max}) and maximal exercise (100 % P_{max}) conditions. Data are presented as the mean with standard deviations.

Regression analysis

Maximum oxygen uptake. A strong linear relationship was found between absolute ($p<0.001$) and relative ($p<0.001$) values for $\dot{V}O_{2max}$ and $\dot{Q}_{max}$ (Fig. 4 A). The slope of the respective regression line indicates that an increase in $\dot{Q}_{max}$ by 1 L between different individuals was associated with an increase in $\dot{V}O_{2max}$ by 84 $mL \cdot min^{-1}$. $\dot{V}O_{2max}$ was also strongly related to BV_{rest} and BV_{max}, while the relation to BV_{max} tended to be slightly stronger than that to BVrest ($r=0.69$ vs. $r=0.65$, both $p<0.001$, Tab. 4). The relationship between $\dot{V}O_{2max}$ and $avDO_2$ was not significant, while the anatomical parameters HV, LVMM and Hbmass significantly correlated with $\dot{V}O_{2max}$ (all $p<0.05$, see Tab. 4). When the abovementioned variables were normalized to both body mass and lean body mass, the relationships were still significant (see Tab. 4).

Tabelle 3. Cardio-circulatory data at rest, 60 % of P_{max} and P_{max}

	$\dot{V}O_2$ ($mL \cdot min^{-1}$)	$\dot{Q}$ ($L \cdot min^{-1}$)	SV (mL)	HR (bpm)	$avDO_2$ ($mL \cdot dL^{-1}$)	CaO_2 ($mL \cdot dL^{-1}$)	SpO_2 (%)	$[Hb]_{ven}$ ($g \cdot dL^{-1}$)
Rest	-	6.2 ± 1.8	94 ± 15.2	65 ± 11.1	-	20.3 ± 0.7	97.5 ± 0.7	15.0 ± 0.7
60% $\dot{V}O_{2max}$	3150 ± 350	21.0 ± 3.1***	150 ± 27.4***	142 ± 11.0***	15.0 ± 1.2	20.4 ± 0.8	94.5 ± 2.1***	15.5 ± 0.5***
100% $\dot{V}O_{2max}$	4624 ± 484#	26.1 ± 4.4***/#	147 ± 30.4	189 ± 8.7***/#	17.9 ± 1.7#	20.6 ± 1.1	91.4 ± 3.2***/#	16.2 ± 0.6***/#

The data are presented as the means±standard deviations. $\dot{V}O_2$=oxygen uptake, $\dot{Q}$=cardiac output, SV=stroke volume, HR=heart rate, $avDO_2$=arterio-venous oxygen difference, CaO_2=arterial oxygen content, SpO_2=peripheral oxygen saturation, $[Hb]_{ven}$=venous hemoglobin concentration (*significant compared to the resting values, $p<0.05$, #significant compared to 60% $\dot{V}O_{2max}$, $p<0.05$).

Cardiac output and stroke volume in relation to blood volume and cardiac size

The cross-sectional data show that $\dot{Q}_{max}$ was strongly correlated with SV_{max} but was also negatively correlated with HR_{max} (see Tab. 4). SV_{max} was similarly related to HV and BV_{max} (Tab. 4). According to the slope of the regression line, an increase in BV_{max} by 1000 mL was associated with an increase in SV_{max} by 25.1 mL, and an increase in HV by 100 mL increased SV_{max} by 6 mL. BV_{rest} was significantly correlated with HV ($p=0.002$, Fig. 4 B), indicating that an increase in BV_{rest} by 1000 mL was associated with an increase in HV by 179 mL. Concerning the significant relationship between BV_{max} and $\dot{Q}_{max}$ ($p<0.001$, Fig. 4 C), an increase in BV_{max} by 1000 mL was associated with an increase in $\dot{Q}_{max}$ by 3.5 $L \cdot min^{-1}$. Applying these cross-sectional data to the intra-individual changes in BV during exercise, the 8 % reduction found in this study would lead to a decrease in $\dot{Q}_{max}$ by 1.6 $L \cdot min^{-1}$ and thus 133 $mL \cdot min^{-1}$ in $\dot{V}O_{2max}$. LVEDD and LVMM were significantly correlated with BV_{max}, SV_{max} and Q_{max}. SpO_2 was not related to the absolute values of $\dot{Q}_{max}$; however, there were, however, significant correlations to $\dot{Q}_{max}$ when normalized to body mass and lean body mass (see Tab. 4).

Tabelle 4. Pearson's product-moment correlations (r) and level of significance (p) between absolute and body mass normalized $\dot{V}O_{2max}$ and cardio-circulatory variables.

		absolute		**relative**			
				·kg^{-1}		**·kg^{-1} LBM**	
		r	p	r	p	r	p
$\dot{V}O_{2max}$ (L·min^{-1})	$\dot{Q}_{max}$ (L·min^{-1})	0.76	<0.001	0.75	<0.001	0.66	<0.001
	SV_{max} (mL)	0.71	<0.001	0.72	<0.001	0.55	0.005
	HV (mL)	0.68	0.002	0.46	0.04	0.45	0.03
	LVEDD (mm)	0.30	0.18	0.56	0.006	0.47	0.03
	LVMM (g)	0.58	0.003	0.43	0.03	0.38	0.06
	Hbmass (g)	0.67	0.002	0.59	0.008	0.43	0.04
	BV_{rest} (mL)	0.65	0.001	0.63	0.001	0.40	0.06
	BV_{max} (mL)	0.69	0.002	0.61	0.004	0.45	0.04
	$avDO_{2max}$ (mL·dL^{-1})	−0.08	0.71	0.03	0.90	0.04	0.87
	ΔSpO_{2max} (%)	−0.42	0.04	−0.37	0.08	−0.29	0.17
	HR_{max} (bpm)	−0.14	0.51	−0.35	0.09	−0.38	0.07
$\dot{Q}_{max}$	HV (mL)	0.64	0.001	0.49	0.02	0.49	0.02
(L·min^{-1})	BV_{rest} (mL)	0.64	0.001	0.50	0.01	0.42	0.04
	BV_{max} (mL)	0.68	0.001	0.54	0.009	0.46	0.03
	SV_{max} (mL)	0.96	<0.001	0.94	<0.001	0.93	<0.001
	ΔSpO_{2max} (%)	−0.58	0.005	−0.66	<0.001	−0.57	0.005
	HR_{max} (bpm)	−0.53	0.007	-	-	-	-
	LVMM (g)	0.44	0.03	0.25	0.26	0.21	0.33
SV_{max}	BV_{rest} (mL)	0.65	0.001	0.45	0.03	0.40	0.05
(mL)	BV_{max} (mL)	0.70	<0.001	0.53	0.01	0.49	0.02
	HV (mL)	0.66	0.001	0.50	0.01	0.51	0.01
	LVEDD (mm)	0.43	0.004	0.31	0.15	0.25	0.24
	LVMM (g)	0.52	0.01	0.32	0.14	0.32	0.13
HV	BV_{rest} (mL)	0.73	0.002	0.52	0.02	0.55	0.007
(mL)	BV_{max} (mL)	0.77	<0.001	0.61	0.03	0.65	0.001
	LVEDD (mm)	0.61	0.003	0.36	0.10	0.37	0.08
LVEDD	BV_{rest} (mL)	0.63	0.001	0.55	0.006	0.51	0.01
(mm)	BV_{max} (mL)	0.58	0.006	0.50	0.02	0.25	0.05

LBM=lean body mass, $\dot{V}O_{2max}$=maximum oxygen uptake, $\dot{Q}_{rest}$= cardiac output at rest, $\dot{Q}_{max}$=maximum cardiac output, SV_{rest}=stroke volume at rest, SV_{max}=maximum stroke volume, HV=heart volume, Hbmass=hemoglobin mass, BV_{max}=blood volume at maximum exercise, $avDO_{2max}$=arteriovenous oxygen difference at maximum exercise, LVEDD=left ventricular end-diastolic diameter, LVMM=left ventricular muscle mass, SpO_{2max}=peripheral oxygen saturation at maximum exercise.

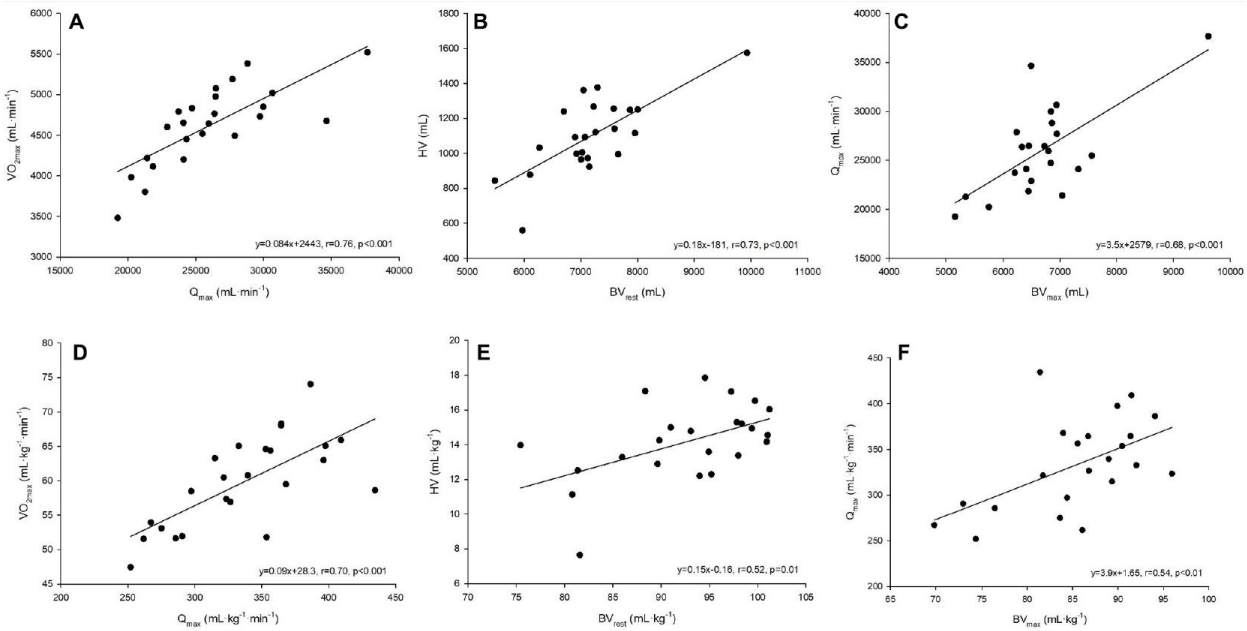

Abbildung 4. Linear regressions analysis between absolute and relative values for maximum oxygen uptake and maximum cardiac output (A, D), heart volume and blood volume at rest (B, E) and maximum cardiac output and blood volume at maximum exercise (C, F).

Discussion and Conclusion

The main goals of this study were to determine the relationships between (i) BV, HV, $\dot{Q}_{max}$ and $\dot{V}O_{2max}$, (ii) to quantify the BV shifts occurring during submaximal and maximal exercise and (iii) to evaluate the effects of these volume shifts on $\dot{Q}_{max}$ and arterial oxygen transport capacity in healthy heterogeneously trained males. The major findings of the cross-sectional study showed that an elevated BV_{max} by 1000 mL was associated with an increase in SV_{max} by approximately 25 mL, leading to an increase in $\dot{Q}_{max}$ by approximately 3.5 $L \cdot min^{-1}$. As BV significantly decreased from rest to maximal exercise by 567 mL (8 %), we calculate a possible limitation in $\dot{Q}_{max}$ by 1.6 $L \cdot min^{-1}$, but we also demonstrate a consistent oxygen transport capacity due to the increase in hemoconcentration.

Stroke volume and heart rate

SV is the most important, strongly blood volume-dependent component of the cardio-circulatory response during exercise *(18)*. In our study, SV increased by 60 % from resting to submaximal exercise conditions. These values are higher than those that were reported during progressive exercise in healthy, untrained subjects *(85,118,119)* and lower than those reported in highly trained endurance athletes *(26)*. According to Vella & Robergs *(19)* there are four main types

of SV responses with increasing exercise intensity. While the mean values for SV in this study showed no significant changes from submaximal to maximal exercise, substantial variability was found among subjects, indicating a progressive increase, plateau formation or a decrease in SV on the individual level. These variations in the SV response from 60 % to 100 % P_{max} were not correlated to $\dot{V}O_{2max}$.

HR_{max} was negatively related to $\dot{V}O_{2max}$ and $\dot{Q}_{max}$ (Tab. 4), which corresponds with previous results *(120)*. With regard to the strong correlation between $\dot{Q}_{max}$ and SV_{max}, these findings demonstrate that, at least near maximal performance, inter-individual differences in $\dot{Q}$ result primarily from variations in SV in both trained and untrained subjects.

Blood volume and cardiac output

As demonstrated by Bonne et al. *(76)*, early increases in $\dot{V}O_{2max}$ following 6 weeks of endurance training are reverted to pretraining levels when the training-induced gains in BV are eliminated by means of phlebotomy, which indicates that total BV is the most important factor of the SV response in early adaptations. However, in a recent study it was demonstrated that the increase in $\dot{V}O_{2peak}$ following 10 weeks of endurance training was preserved even after Hbmass and BV were reversed to pretraining levels by phlebotomy, thereby contradicting the assumption that improvements in $\dot{V}O_{2peak}$ and $\dot{Q}_{peak}$ are exclusively attributed to BV expansion *(77)*. In their comprehensive review, Lundby et al. revealed the underlying mechanisms of improvements in $\dot{V}O_{2max}$ *(5)*. Increases in SV at rest and during exercise are mainly dependent on increased venous return as a result of a high BV leading to higher end-diastolic volumes via the Frank-Starling mechanism. As we found significant correlations between $\dot{Q}_{max}$ and BV_{max} (Fig. 4 C and F), we hereby confirmed these mechanisms for our heterogeneously trained population included in this study. Moreover, we demonstrated the quantitative effect of an expanded BV: Male subjects with a BV of ~5 L are able to achieve a $\dot{Q}_{max}$ of ~20 L·min^{-1}. A change in BV by 1 L was related to a change in $\dot{Q}_{max}$ by ~3.5 L·min^{-1}. This indicates that when the BV is increased, e.g. by 2.5 L as a result of a higher training status *(74)*, $\dot{Q}_{max}$ is increased considerably to 28.8 L·min^{-1}. As an increase in $\dot{Q}_{max}$ by 1 L is associated with an increase in $\dot{V}O_{2max}$ by ~84 mL·min^{-1}, information on increases in BV is particularly important. All these considerations are also valid for the relative values and prove a mechanism that is independent of the anthropometric conditions (see Fig. 4 D-F and Tab. 4). From a practical point of view, the question remains whether changes in BV caused by environmental conditions influence $\dot{Q}_{max}$ and therefore $\dot{V}O_{2max}$. At high altitude, a lower $\dot{Q}_{max}$ also refers to a plasma volume reduction *(121)*,

while during heat adaptation plasma volume expansion may increase $\dot{Q}_{max}$. This view is supported by Kanstrup & Ekblom, who demonstrated that an increase in PV by a 700 mL dextran infusion augments SV at rest and throughout exercise and therefore $\dot{Q}$ *(122)*. In terms of favorable changes in $\dot{V}O_{2max}$ following heat training, there is still a lack of evidence in the literature *(82,123)*.

Concerning the regulation of SV and thus $\dot{Q}_{max}$, our results support the hypothesis that total BV seems to be the major determinant of the SV response during exercise. BV expansion occurring during long-term training periods *(124)* may therefore represent an important part of cardiocirculatory adaptation to physical training. On the other hand, it is also important to consider that absolute BV may sometimes be of limited value to determine its impact on hemodynamics during exercise. Even more important is the hemodynamically active blood volume, i.e., the proportion of the total BV that affects pressure, flow, and cardiac function. This hemodynamically active BV would allow a high SV_{max} and thus $\dot{Q}_{max}$ despite a relatively small absolute BV *(78)*. In any case, however, we assume that a large resting BV provides a beneficial precondition for a high hemodynamically active BV.

Blood volume and heart volume

When untrained subjects were matched to trained endurance athletes in terms of BV via dextran infusion, an increase in SV during exercise in the untrained group was observed, but these values were still lower than those in the trained athletes *(79)*. This finding indicates that BV alone cannot explain the differences in SV, suggesting that a larger HV has to accompany a larger BV *(76)* which is clearly demonstrated by the strong relationship between BV and HV in this study (Fig. 4 B). To date, very few studies have investigated the relationship between BV and cardiac size in healthy adults. It is widely accepted that increased end-diastolic dimensions of the right and left ventricles, increased LVMM, and increased volume of the left atrium are now well-established hallmarks of what has been defined as the athlete's heart *(80)*. However, these structural parameters have rarely been correlated with the prevailing BV, and there do not exist any data on the relationship between HV and BV. The magnitude of the HV is approximately 15 % of the BV, and in our study, too, a change in the BV was associated with an approx. 15 % change in the HV, which indicates a similar adjustment in both structures. In addition, we found LVMM to be significantly correlated with resting BV. Since the hemodynamic changes that occur during exercise constitute the primary stimulus for cardiac remodeling *(80)*, it is reasonable to assume that high BV again plays a major role in these adaptations. As already mentioned above and regarding BV_{max} and $\dot{Q}_{max}$, the relationship between BV and HV applies

regardless of the anthropometric conditions and thus represents the likely coupled adaptation processes to long-term training stimuli (see Fig. 4 B and E).

Blood volume shifts

This is one of the very few studies in which exercise-induced decreases in total BV were quantified during exercise. While the percentage changes in BV were calculated based on the changes in [Hb] and hematocrit in previous studies *(110)*, our results showed an absolute mean reduction of 567 mL in this population. These findings are larger than those found by Wilkerson et al. who found a mean reduction of 363 mL at $\dot{V}O_{2max}$ *(125)* but comparable with the 532 mL reduction reported by Kawabata et al. *(36)*. The decrease in plasma volume, which becomes obvious by the accompanying hemoconcentration, is generally due to a greater filtration rate (caused by an increase in blood pressure), sweat loss (which is of minor importance during short lasting bouts of exercise as in this study), and especially lactate accumulation and the breakdown of creatine phosphate within the muscle cell *(38)*. The latter of which cause an increased osmotic gradient, that, in turn, lead to an influx of water into the intracellular and interstitial space *(41,42)*, thereby increasing the intracellular volume by as much as 15 % *(126)*. While we can confirm earlier results regarding the relationship between the total PV at rest and the amount shifted until maximum exercise *(36)*, it remains unclear whether endurance-trained athletes shift more water into the intracellular space during exercise than untrained subjects. After all, we found no significant relationship between the percentage changes in BV and $\dot{V}O_{2max}$ and no relation with the maximum lactate concentrations, which are thought to be the main cause of these volume shifts *(42,127)*. This suggests that training status does not affect the amount of water shifted to the intracellular space during exercise.

Although one must assume that any decrease in circulating BV affects the SV response during exercise, the mean SV in this population increased from rest to 60 % P_{max} and was not different between 60 % and 100 % P_{max}. The dissociation between the SV and BV response from resting to submaximal values (Fig. 3) can be explained by an increased venous return that by far outmatches the BV shifts *(128)*. However, in regard to a lacking further increase in SV from submaximal to maximal exercise, we can only speculate if these volume shifts might have a potential negative effect. It would be of great interest if volume matched fluid compensation in the extent of the individual volume shifts, i.e., via plasma or dextran infusion during exercise would lead to a greater increase in SV and thus $\dot{Q}_{max}$, hence increasing $\dot{V}O_{2max}$.

Fluid shifts and oxygen transport

Last, not all physiological mechanisms during high-intensity exercise inevitably lead to the optimization of oxygen transport. In this study, the SpO_2 decreased by approximately 6 %, which corresponds to data from e.g. *(107)* who found heterogeneous decreases in SpO_2 in trained and untrained subjects. Our data also indicate a significant decrease in SpO_2 with increasing $\dot{V}O_{2max}$. This might be due to a larger $\dot{Q}_{max}$ in the trained subjects (see Tab. 4), resulting in higher pulmonary blood flow and impaired O_2 diffusion in the lungs *(75)*. This view is supported by the significant correlation between SpO_2 and $\dot{Q}_{max}$. Without considering the effects of hemoconcentration and the augmentation of CaO_2 in addition to the known reduction in arterial O_2 saturation, the reduction in BV may decrease $\dot{Q}_{max}$ and thus the maximum oxygen transport. Regarding the results from the cross-sectional part of this study, the reduction in BV by 567 mL might have reduced $\dot{Q}$ by 1.6 $L \cdot min^{-1}$ and thereby $\dot{V}O_{2max}$ by 133 $mL \cdot min^{-1}$ during the performance test. These considerations, however, assume that organ perfusion remains constant despite the reductions in BV, which needs further investigation that would require the inclusion of parameters such as mean arterial pressure or vascular resistance.

All previous considerations have assumed that a change in hemoconcentration is accompanied by a change in arterial oxygen content. In this study, [Hb] increased by 1.3 $g \cdot dL^{-1}$ (8.5 %) until maximum exercise, which, in theory would lead to an increase in CaO_2 by 1.8 $mL \cdot dL^{-1}$. However, SpO_2 simultaneously decreased by 6.1 % so that the arterial O_2 content even tended to increase (see Tab. 3). When comparing the amount of O_2 that is transported per minute either with or theoretically without the effects of the fluid shifts on $\dot{Q}_{max}$ and the corresponding hemoconcentrations, the result is 5376 $mL \cdot min^{-1}$ (with hemoconcentration, see Tab. 3) and 5208 $mL \cdot min^{-1}$ (without hemoconcentration), respectively. These findings indicate that the fluid shifts completely compensate for the decrease in SpO_2 and the reduced $\dot{Q}_{max}$. Similar to acute altitude effects, the hemoconcentration due to transient plasma volume shifts could, therefore, be interpreted as a physiological adjustment to maintain oxygen transport capacity, without compromising performance.

Limitations

Since we only conducted linear regression analysis, we cannot confirm cause and effect relationships; however, we can draw general conclusions. For the calculation of the possible effects of blood volume changes during exercise, we partly use data from the regression analyses obtained in the cross-sectional study which is based on a very heterogeneous group of test subjects.

Therefore, the results must be considered with caution, even though they certainly show physiological trends. Direct manipulations of BV must be applied to compare the effects of volume shifts with fluid compensated conditions on hemodynamic mechanisms. To determine whether the increase in hemoconcentration and consequently maintained CaO_2 really are fully compensatory for the reductions in $\dot{Q}$ discussed here, additional data such as blood flow to working muscle, mean arterial pressure and vascular resistance (since blood pressure was not measured) should also be collected to draw a more holistic conclusion. Whether the compensated CaO_2 due to hemoconcentration influences a regulatory feedback mechanism on the $\dot{Q}_{max}$, as considered possible by Calbet *(109)*, cannot be explained by the results of the present study.

The determination of cardiac output with the Innocor system is relatively precise during exercise testing in our lab with a TE of 4.9 %, which is comparable to previous investigations *(112)*. However, it only allows hemodynamic measurements at limited time intervals, making it somewhat difficult to draw a comprehensive conclusion on the precise time course of physiologic regulations. This is of special importance in interpreting the four types of SV responses according to Vella and Robergs *(19)*. Depending on the time of measurement at least three measurements during exercise are necessary to identify the individual responses. Other systems that allow continuous hemodynamic measurements should therefore be considered in future studies.

Conclusion

We found a strong correlation between BV_{max} and $\dot{Q}_{max}$, suggesting that an increase in BV_{max} by 1 L is associated with an increase in $\dot{Q}_{max}$ by ~3.5 $L \cdot min^{-1}$. Additionally, HV was closely correlated with BV_{rest}, indicating that a change in BV by 1 L is correlated with a change in HV by 179 mL. Mean BV significantly decreased until maximum exercise by 567 mL. We hypothesize that the exercise-induced reductions in total BV may have detrimental effects on the $\dot{Q}_{max}$ response, as this value might have changed by as much as 1.6 $L \cdot min^{-1}$ in our study. On the other hand, [Hb] increased by 1.3$g \cdot dL^{-1}$ due to fluid shifts, thereby maintaining CaO_2, which completely compensates for the exercise induced arterial desaturation. Our results support the general conviction that a high BV at rest is needed in order to achieve a high $\dot{Q}_{max}$. Blood volume shifts during intense exercise may have a detrimental effect on $\dot{Q}$, but at the same time, they exert a beneficial effect on the oxygen transport system. This effect may maintain a reasonable $avDO_2$, and thereby overcompensates for the negative effects on $\dot{Q}_{max}$.

7 Artikel II: Cardiac Stroke Volume in Females and its Correlation to Blood Volume and Cardiac Dimensions

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Abstract

We aimed to continuously determine the stroke volume (SV) and blood volume (BV) during incremental exercise to evaluate the individual SV course and to correlate both variables across different exercise intensities. Twenty-six females with heterogeneous endurance capacities performed an incremental cycle ergometer test to continuously determine the oxygen uptake ($V\dot{O}_2$), cardiac output ($\dot{Q}$) and changes in BV. $\dot{Q}$ was determined by impedance cardiography and resting cardiac dimensions by 2D echocardiography. Hemoglobin mass and BV were determined using a carbon monoxide-rebreathing method. $V\dot{O}_{2max}$ ranged from 32 to 62 mL·min^{-1}·kg^{-1}. $\dot{Q}_{max}$ and SV_{max} ranged from 16.4 to 31.6 L·min^{-1} and 90 to 170 mL, respectively. The SV significantly increased from rest to 40 % and from 40 % to 80 % $\dot{V}O_{2max}$. Changes in SV from rest to 40 % $\dot{V}O_{2max}$ were negatively ($r = -0.40$, $p = 0.05$), between 40 % and 80 % positively correlated with BV ($r = 0.45$, $p < 0.05$). At each exercise intensity, the SV was significantly correlated with the BV and the cardiac dimensions, i.e., left ventricular muscle mass (LVMM) and end-diastolic diameter (LVEDD). The BV decreased by 280 ± 115 mL (5.7 %, $p = 0.001$) until maximum exercise. We found no correlation between the changes in BV and the changes in SV between each exercise intensity. The hemoglobin concentration [Hb] increased by 0.8 ± 0.3 g·dL^{-1}, the capillary oxygen saturation (ScO_2) decreased by 4.0 % ($p < 0.001$). As a result, the calculated arterial oxygen content significantly increased (18.5 ± 1.0 vs. 18.9 ± 1.0 mL·dL^{-1}, $p = 0.001$). A 1 L higher BV at $\dot{V}O_{2max}$ was associated with a higher SV_{max} of 16.2 mL ($r = 0.63$, $p < 0.001$) and $\dot{Q}_{max}$ of 2.5 L·min^{-1} ($r = 0.56$, $p < 0.01$). In conclusion, the SV strongly correlates with the cardiac dimensions, which might be the result of adaptations to an increased volume load. The positive effect of a high BV on SV is particularly noticeable at high and severe intensity exercise. The theoretically expected reduction in $\dot{V}O_{2max}$ due to lower SV as a consequence of reduced BV is apparently compensated by the increased arterial oxygen content due to a higher [Hb].

Keywords: cardiac output, oxygen uptake, echocardiography, impedance cardiography, hemodynamics, hemoconcentration, plasma volume shifts, carbon monoxide-rebreathing

Introduction

It is generally accepted that the variation in maximal stroke volume (SV_{max}) is mostly responsible for the range of maximum oxygen uptake ($\dot{V}O_{2max}$) values in healthy, trained and untrained men and women *(4,5,99)*. Although it has been shown that endurance trained athletes possess higher absolute SV_{max} values for a given body dimension *(129–131)*, there is still an ongoing debate about the course of the SV during dynamic exercise. Specifically, it is a question whether the SV increases until termination of exercise in healthy individuals or at maximum intensity (i.e., 10–30 s before exhaustion) the SV is lower than the values observed at submaximal intensities due to a regulatory limit of the heart *(21,22)*. However, these conclusions often come from studies that either compared resting to maximum values and/or further included only a single value during submaximal conditions. This circumstance is often due to the methodological difficulties in the continuous determination of cardiac output ($\dot{Q}$). However, it is well known that the SV can demonstrate different individual courses *(19)*, which makes it necessary to include several measurement points and thus a continuous monitoring. It has been repeatedly demonstrated that higher SVs are typically the result of larger cardiac dimensions, an enhanced venous return and cardiac preload. The latter is mostly due to a genetically predetermined and/or training-induced larger blood volume (BV) *(66,85,119,132)*. In this context, it must be noted that the BV substantially decreases during incremental exercise *(36,82)*, thus possibly exerting a negative impact on the SV course during progressive exercise. At the same time, however, these volume shifts also have a beneficial impact on the oxygen transport capacity due to the increase in hemoglobin concentration as we were recently able to demonstrate *(133)*. Basic structural cardiac properties including left ventricular (LV) hypertrophy as result of endurance training also contribute to the ability to continuously increase the SV throughout exercise especially in endurance trained athletes *(134–136)*. Since there is an interaction between the hemodynamic changes that occur during exercise and the cardiac dimensions, e.g., as seen in eccentric cardiac remodelling after chronic volume overload following endurance training *(80,137)*, both cardiac dimensions and BV need to be investigated in addition to the aforementioned continuous SV monitoring to detect underlying mechanisms for different SV courses during dynamic exercise. To the best of our knowledge, this has not yet been done. Therefore, the aims of this study were 1) to continuously evaluate the individual SV and BV course across different exercise intensities, 2) evaluate the correlation between cardiac dimensions and SV and BV at rest and during exercise, respectively and 3) to quantify exercise-induced BV shifts and estimate their influence on the SV and arterial oxygen content (CaO_2) during incremental cycle exercise.

Methods

Participants

Twenty-six healthy, nonsmoking females with heterogeneous endurance capacities and without history of cardiac disease were included in the study (see Table 5 for subject characteristics). The participants provided written consent after they were informed about the content of the study, the associated risks and the possibility to withdraw without indication of any reason. The study was conducted in conformity with the declaration of Helsinki and Good Clinical Practice and the study protocol was approved by the ethics committee of the University of Bayreuth in Germany (O 1305/1 – GB).

Tabelle 5. Subject characteristics (n=26).

	Mean ± SD	**Min**	**Max**	**95 % CI**
Age (y)	27.5 ± 5.9	19	40	25.1 - 29.9
Height (cm)	167.7 ± 6.5	154	180	165 - 170
Body mass (kg)	60.1 ± 7.0	47.5	73.5	58.1 - 63.9
BSA (m^2)	1.69 ± 0.1	1.43	1.88	1.64 - 1.74
BMI ($kg \cdot m^{-2}$)	21.6 ± 1.6	18.6	25.1	20.9 - 22.3
Lean body mass (kg)	47.4 ± 5.9	35.9	56.9	44.9 - 49.9
Fat mass (%)	22.2 ± 5.6	9.4	35.0	19.8 - 24.6
Ferritin ($\mu g \cdot L^{-1}$)	44 ± 24	16	105	34.2 - 54.0

The data are presented as the arithmetic mean ± standard deviation. Min=minimum, Max=maximum, CI=confidence interval, BSA=body surface area, BMI=body mass index.

Study design

The participants performed an incremental cycle ergometer test during which the SV and $\dot{V}O_2$ were continuously measured. Simultaneously, the hemoglobin concentration for the calculation of BV and capillary O_2 saturation (ScO_2) were determined. Prior to the performance test, anthropometric measurements including body composition were conducted using a bioelectrical impedance analysis. A cubital venous blood sample was drawn to determine hematological variables and ferritin concentrations to exclude any iron deficiencies. The cardiac dimensions were determined by 2D echocardiography and the hemoglobin mass was measured twice on consecutive days and within 7 days after the ergometer test using a carbon monoxide-rebreathing method.

Anthropometric measurements and analytical procedures

Prior to the exercise test, lean body mass and fat mass were measured twice consecutively and arithmetically averaged using a bioelectrical impedance analysis (InBody 770, InBody Co., Seoul, South Korea). The body surface area was calculated according to Dubois and Dubois *(138)*. Cubital venous blood samples (8 mL) were drawn after the participants rested for 15 min in a seated position. These heparinized blood samples were analysed using a fully automated haematology system (Sysmex XN 1000-1-A, Sysmex, Norderstedt, Germany) for red blood cells including hemoglobin concentration ([Hb]) and hematocrit (Hct). In the serum, the ferritin and C-reactive protein (CRP) concentrations were determined by enzyme immunoassays [ferritin: LKFE1, CRP highly sensitive: LKCRP1 (ELISA & Immulite 1,000, Siemens Healthcare Diagnostics GmbH, Erlangen, Germany)].

Incremental ergometer test

Maximum power output (P_{max}) was determined using an incremental protocol on a cycle ergometer (Excalibur Sport, Lode, Groningen, Netherlands). After a 3-min warm-up phase of 50 W, the mechanical power output was increased by 50 W every 3 min (stepwise by 17, 17 and 16 W per minute) until subjective exhaustion was reached. The oxygen uptake ($\dot{V}O_2$) was determined via breath-by-breath technology (Metalyzer 3B, Cortex, Leipzig, Germany) and the maximum $\dot{V}O_2$ ($\dot{V}O_{2max}$) was calculated as the highest 30-s interval before exhaustion. In our analyses the values for $\dot{V}O_2$ were scaled to body mass as a standard reference and also to body mass to the power of −0.73 *(139)*. Capillary blood samples were taken from a hyperemized earlobe to quantify the lactate concentrations before exercise, every 3 min during exercise, immediately at exhaustion and 1, 3, 5 and 7 min after exhaustion (Biosen S-Line, EKF-Diagnostic, Barleben, Germany). Additional capillary blood samples were taken before exercise, every 3 min during exercise and immediately at exhaustion for the measurement of capillary oxygen saturation (ScO_2, OSM III hemoximeter, Radiometer, Copenhagen, Denmark) and hemoglobin concentration ([Hb]) using a standardized and calibrated photometric analysis (HemoCue 201, HemoCue AB, Ängelholm, Sweden). Arterial oxygen content (CaO_2) was calculated according to the following formula where 1.39 = Huefner number:

$$CaO_2\ (mL \cdot \mathrm{dL}^{-1}) = [Hb]\ (g \cdot \mathrm{dL}^{-1}) \times SpO_2\ (\%) \div 100 \times 1.39 \qquad (1)$$

Calculation of cardiac output and arteriovenous oxygen difference during exercise

Stroke volume (SV) and cardiac output ($\dot{Q}$) were measured continuously during exercise using a portable, battery powered and non-invasive cardiac monitoring device with signal morphology-based impedance cardiography (PhysioFlow Enduro, Manatec Biomedical, Paris, France). For a detailed description of the method see here *(71)*. The values were continuously measured and averaged over 5-s intervals. For further analyses, four 5-s intervals were averaged for the calculation of the mean SV at the respective exercise intensities, i.e., 40 % ($SV_{40\%}$), 60 % ($SV_{60\%}$), 80 % ($SV_{80\%}$) and 100 % $\dot{V}O_{2max}$ ($SV_{100\%}$). Similarly, 5-s averages of SV data were aligned to absolute $\dot{V}O_2$ corresponding to 1.0, 1.5, 2.0, 2.5, 3.0 and 3.5 $L \cdot min^{-1}$. Based on the mean SV at a specific exercise intensity, we also calculated the changes in SV between exercise intensities, e.g., between SV_{rest} and $SV_{40\%}$ ($\Delta SV_{R\text{-}40\%}$) or $SV_{40\%}$ and $SV_{80\%}$ ($\Delta SV_{40–80\%}$). The highest SV (SV_{max}) was calculated as the highest 20-s interval before exhaustion. Prior to the exercise, one investigator measured blood pressure using a professional blood pressure monitor (HBP-1300-E, Omron Healthcare Co., Ltd., Kyoto, Japan) with the participant seated and at rest on the cycle ergometer. Systolic and diastolic blood pressure were measured three times with the last two measures averaged for entry into the autocalibration process of the PhysioFlow system. The arterio-venous oxygen difference ($avDO_2$) was calculated according to the Fick principle, in which it represents the quotient of $\dot{V}O_2$ and $\dot{Q}$. The PhysioFlow impedance cardiography was found to have an acceptable standard error of measurement of 3.96 at 70 % of P_{max} *(140)*.

Determination of hemoglobin mass and total blood volume

At least 2 h after the incremental test, when the plasma volumes had returned to pre-exercise values *(113)*s, the total hemoglobin mass (Hbmass), total blood (BV), plasma (PV) and erythrocyte (RCV) volumes were determined using a carbon monoxide (CO)-rebreathing method according to previous investigations *(50,51,114)*. In brief, an individual dose of CO (0.8–0.9 $mL \cdot kg^{-1}$, CO 3.7, Linde AG, Unterschleißheim, Germany) was administered and rebreathed along with 3 L of pure medical oxygen (Med. O_2 UN 1072, Rießner-Gase GmbH, Lichtenfels, Germany) for 2 min. Capillary blood samples were taken before and 6 and 8 min after the administration of the CO dose. In the blood samples %HbCO was measured using an OSM III hemoximeter (Radiometer, Copenhagen, Denmark). The Hbmass was calculated based on the mean change in %HbCO before and after the CO was rebreathed. As part of the equation to

calculate changes in BV during the exercise period, the capillary [Hb] was measured and converted to the venous conditions *(115,117)*. The BV was then calculated according to the following formula where 0.91 = cell factor at sea level *(52)*:

$$BV\ (mL) = Hbmass\ (g) \times 100 \div [Hb]\ (g \cdot \mathrm{dL}^{-1}) \div 0.91 \quad (2)$$

The BV was calculated at rest (BV_{rest}) and for different percentages of $\dot{V}O_{2max}$ ($BV_{40\%}$, $BV_{60\%}$, $BV_{80\%}$, $BV_{100\%}$). For the calculation of the submaximal BV the [Hb], which were determined at rest and every 3 min during exercise, were interpolated for the respective percentages of $\dot{V}O_2$, if necessary. We also calculated the exercise-induced changes in BV between the different exercise intensities, i.e., between BV_{rest} and $BV_{40\%}$ ($\Delta BV_{R\text{-}40\%}$), BV_{40} and $BV_{60\%}$ ($\Delta BV_{40–60\%}$), BV_{60} and $BV_{80\%}$ ($\Delta BV_{60–80\%}$), $BV_{80\%}$ and $BV_{100\%}$ ($\Delta BV_{80–100\%}$) and BV_{rest} and $BV_{100\%}$ ($\Delta BV_{R\text{-}100\%}$). Since the Hbmass does not change over short periods of time *(56)*, the temporally offset determination of the [Hb] for the calculation of the BV is possible without compromising accuracy. For a detailed description and the accuracy of the method see *(50,51,114)*. The typical error for the determination of Hbmass in our laboratory is 1.5 %, which is in line with previous investigations *(116,117)*, while the typical error for BV is 2.5 %.

Echocardiography

Transthoracic two-dimensional echocardiography for resting cardiac dimensions was performed by the same investigator with the participants remaining in a supine position using a cardiology ultrasound system (Philips EPIC 7, Phillips Medical Systems, Andover, MA, United States) with a 1.0–5.0 MHz sector array transducer (Philips S5-1, Phillips Medical Systems, Andover, MA, United States) according to the general recommendations *(141,142)*. The systolic left ventricular ejection fraction (LV-EF) was estimated and calculated using the biplane Simpson rule, based on the apical four- and the apical two-chamber view. Two-dimensional linear dimensions for both ventricles and both atria were performed manually according to previous recommendations *(141,143)*. An estimation of the right ventricular systolic function using the tricuspid annular plane systolic excursion (TAPSE) was obtained in the apical four chamber view. Based on the 2D echocardiographic measurements, the left ventricular muscle mass (LVMM) and index (LVMM index), relative wall thickness (RWT) of the left ventricle and left atrial volume index (LAVI) were calculated with validated methods *(144,145)*. Additionally, each participant was evaluated for the prevalence of right and left heart valve regurgitation as part of the standard echocardiographic assessment with no participant demonstrating abnormalities.

Statistical analysis

The data are presented as means and standard deviations. Statistical analysis was conducted using GraphPad Prism Version 8.0.2 (GraphPad Software, Inc., San Diego, United States) and IBM SPSS Statistics 26 (IBM, Armonk, United States). Testing for normality was performed using the Shapiro-Wilk test. Repeated measures one-way ANOVA or a mixed effects analysis followed by Turkey's multiple comparisons test were performed to find significant differences between the exercise intensities. Pearson's product moment and Spearman correlations as well as simple linear regression analyses were performed to assess the correlations and quantitative dependencies between two variables. The level of significance was set to $p \leq 0.05$.

Results

Performance, hematological and cardiac data showed large interindividual variability (see. Table 6). The $\dot{V}O_{2max}$ ranged between 32 and 62 $mL \cdot min^{-1} \cdot kg^{-1}$. The blood volume at rest (BV_{rest}) and Hbmass ranged between 64 and 97 $mL \cdot kg^{-1}$ and 7.8 and 12.7 $g \cdot kg^{-1}$, respectively. LVEDV and LVEDD ranged between 50 and 150 mL and 32 and 52 mm, respectively. LVMM and LVMM index ranged between 65 and 187 g and 46 and 106 $g \cdot m^{-2}$.

The BV significantly decreased until maximum exercise by 5.7 % (280 ± 115 mL, $p < 0.001$); as a result, [Hb] significantly increased by 0.8 ± 0.3 $g \cdot dL^{-1}$. We found a moderate, yet not significant correlation between the BVrest and the amount of fluid shifted until maximum exercise ($\Delta BV_{R\text{-}100\%}$, $r = 0.38$, $p = 0.06$). The ScO_2 levels decreased by 4.0 % ($p < 0.001$), while the CaO_2 significantly increased from rest to maximum exercise (18.5 ± 1.0 vs. 18.9 ± 1.0 $mL \cdot dL^{-1}$, $p = 0.001$). The HR continuously increased until maximum exercise (184 ± 9.2 bpm). $\dot{Q}$ increased in a linear fashion from 4.5 ± 1.4 $L \cdot min^{-1}$ at rest to 22.8 ± 3.6 $L \cdot min^{-1}$ at $\dot{V}O_{2max}$. The $avDO_2$ significantly increased from 9.4 $mL \cdot dL^{-1}$ at 40 % $\dot{V}O_{2max}$ to 13.1 $mL \cdot dL^{-1}$ at $\dot{V}O_{2max}$ ($p < 0.001$, see Table 7).

Tabelle 6. Performance, hemoglobin mass and cardiological data.

	Mean ± SD	**Min**	**Max**	**95 % CI**
P_{max} (W)	259.3 ± 55.9	117	334	236 - 282
P_{max} ($W \cdot kg^{-1}$)	4.2 ± 0.8	2.3	5.5	3.9 - 4.5
$\dot{V}O_{2max}$ ($mL \cdot min^{-1}$)	2992 ± 589	1620	3960	2754 - 3230
$\dot{V}O_{2max}$ ($mL \cdot min^{-1} \cdot kg^{-0.73}$)	149 ± 25	92	185	139 - 159
Hbmass (g)	597 ± 111	389	843	551 - 642
Hbmass ($g \cdot kg^{-1}$)	9.8 ± 1.2	7.8	12.7	9.3 - 10.3
RER_{max}	1.22 ± 0.06	1.13	1.34	1.19 - 1.24
$[Lac]_{max}$ ($mmol \cdot L^{-1}$)	12.1 ± 2.4	8.5	18.3	11.2 - 13.1
LVESV (mL)	35.3 ± 10.4	16	60	30.9 - 39.6
LVEDV (mL)	100.5 ± 27.8	50	150	88.8 - 112.2
LVEDD (mm)	41.0 ± 4.9	32	52	38.9 - 43.0
LVMM (g)	130 ± 35	65	187	115 - 145
LVMM index ($g \cdot m^{-2}$)	76.7 ± 17.5	46	106	69 - 84
PWd (mm)	9.6 ± 0.9	8	11	9.2 - 9.9
IVSd (mm)	9.9 ± 1.2	8	12	9.4 - 10.4

The data are presented as the means±standard deviations (SD). Min=minimum, Max=maximum, CI=confidence interval, P_{max}=maximum power, $\dot{V}O_{2max}$=maximum oxygen uptake, $\dot{V}O_{2max}$ rel.=relative maximum oxygen uptake, Hbmass=hemoglobin mass, Hbmass rel.=relative hemoglobin mass, RER_{max}=maximum respiratory exchange ratio, $[Lac]_{max}$=maximum lactate concentrations, LVESV=left ventricular endsystolic volume, LVEDV=left ventricular enddiastolic volume, LVEDD=left ventricular enddiastolic diameter, LVMM=left ventricular muscle mass, PWd=left ventricular outflow tract diameter (mm), IVSd= interventricular septal thickness at end-diastole.

Stroke volume response

After an initial increase from rest to 40 % $\dot{V}O_{2max}$ (65 ± 17 mL to 113 ± 18 mL, $p < 0.001$), mean SV significantly further increased from 40 to 80 % $\dot{V}O_{2max}$ (120 ± 18 mL, $p < 0.01$) without significant change until $\dot{V}O_{2max}$ (124 ± 20 mL, see Figure 4 A and Table 7). As Figure 4 A shows, the SV response was highly individual including progressive increases (n = 8), plateaus with (n = 4) and without a secondary increase (n = 6) as well as plateaus with a drop (n = 4). Four participants showed a progressive increase until 80 % $\dot{V}O_{2max}$ followed by a drop in SV. The $\Delta SV_{R\text{-}40}$ and $\Delta S_{V40\text{-}80}$ ranged from 8 to 98 and −7-20 mL, respectively.

The SV_{max} values ranged from 90 to 170 mL. Two participants reached their highest values at 40 % $\dot{V}O_{2max}$, nine at 60 %, five at 80 % and ten at $\dot{V}O_{2max}$. The time point of reaching the SV_{max} was not significantly correlated to the relative $\dot{V}O_{2max}$ or the BV_{rest}, even though for the

latter a trend was observed ($r = 0.37$, $p = 0.06$). Subjects with a $\dot{V}O_{2max} \geq 55$ mL·min^{-1}·kg^{-1} ($n = 7$) showed significantly higher SV values at all exercise intensities ($p < 0.05$) except for maximum exercise when compared to those with lower $\dot{V}O_{2max}$. When related to the same absolute oxygen uptake (Figure 5 B), the magnitude of SV varied largely between participants specifically when absolute $\dot{V}O_{2max}$ was low (e.g., 2000 mL·min^{-1}: 117 ± 17.3 mL). At higher oxygen uptake values the scattering was considerably reduced (e.g., 3.5 L·min^{-1}: 133 ± 10.7 mL).

Tabelle 7. Cardio-pulmonary data at rest and at different percentages of $\dot{V}O_{2max}$.

	Rest	**40 %**	**60 %**	**80 %**	**100 %**
$\dot{V}O_2$ (mL·min^{-1})	-	1193 ± 233	1789 ± 350*	2385 ± 466$^{*/\#}$	2991 ± 589$^{*/\#}$
$\dot{V}O_2$ (mL·kg^{-1}·min^{-1})	-	19.5 ± 3.2	29.3 ± 4.8$^{*/\#}$	39.1 ± 6.4$^{*/\#}$	49.0 ± 8.1$^{*/\#}$
$\dot{Q}$ (L·min^{-1})	4.5 ± 1.4	12.7 ± 2.7*	16.1 ± 2.9$^{*/\#}$	19.3 ± 3.0$^{*/\#}$	22.8 ± 3.6$^{*/\#}$
$\dot{Q}$ (mL·kg^{-1}·min^{-1})	75 ± 21	211 ± 53*	269 ± 58$^{*/\#}$	319 ± 57$^{*/\#}$	377 ± 58$^{*/\#}$
SV (mL)	65 ± 17	113 ± 18*	116 ± 19	120 ± 18$^{\#}$	124 ± 20$^{\#}$
SV (mL·kg^{-1})	1.07 ± 0.24	1.87 ± 0.35*	1.93 ± 0.35	1.98 ± 0.33$^{\#}$	2.05 ± 0.32$^{\#}$
HR (1·min^{-1})	69 ± 12	112 ± 15*	139 ± 14$^{*/\#}$	161 ± 11$^{*/\#}$	184 ± 9$^{*/\#}$
$avDO_2$ (mL·dL^{-1})	-	9.4 ± 2.8	11.1 ± 2.6$^{*/\#}$	12.4 ± 2.3$^{*/\#}$	13.1 ± 2.1$^{*/\#}$
$\Delta BV_{R\text{-}100\%}$ (mL)	-	−54 ± 56*	−173 ± 88$^{*/\#}$	−196 ± 105$^{*/\#}$	−280 ± 115$^{*/\#}$

The data are presented as the means ± standard deviations. $\dot{V}O_2$=oxygen uptake, $\dot{Q}$=cardiac output, SV=stroke volume, HR=heart rate, $avDO_2$=arteriovenous oxygen difference, $\Delta BV_{R\text{-}100\%}$=changes in BV compared to resting conditions (*significant compared to previous intensity, $^{\#}$significant compared to 40 % $\dot{V}O_{2max}$, $p < 0.05$).

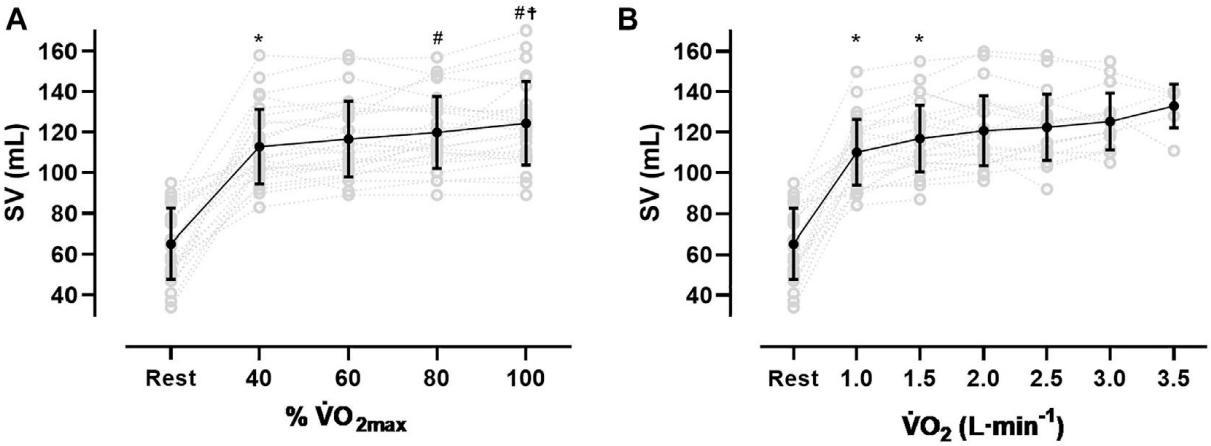

Abbildung 5. Stroke volume (SV) response from rest to $\dot{V}O_{2max}$ (A) and at the same absolute $\dot{V}O_2$ (B), *sig. compared to previous condition, $^{\#}$compared to 40 % $\dot{V}O_{2max}$, †compared to 60 % $\dot{V}O_{2max}$.

Correlation and regression analysis

SV vs. BV

SV_{rest} was significantly correlated to BV_{rest} (r = 0.70, p = 0.0001), however, the correlation between $SV_{40\%}$ and $BV_{40\%}$ was not significant. The correlations between $SV_{60\%}$ and $BV_{60\%}$ (r = 0.41, p < 0.05), $SV_{80\%}$ and $BV_{80\%}$ (r = 0.51, p < 0.01), $SV_{100\%}$ and $BV_{100\%}$ (r = 0.55, p < 0.01), as well as SV_{max} and $BV_{100\%}$ (r = 0.63, p < 0.001) were all significant. When these values were related to BSA, the correlations between the SV_{rest} and BV_{rest} (r = 0.59, p < 0.01) and SV_{max} and $BV_{100\%}$ (r = 0.42, p < 0.05) were still significant, whereas no correlations were found for the submaximal intensities. When the SV at different absolute $\dot{V}O_{2max}$ (0.5-3 $L \cdot min^{-1}$, see Figure 5 B) were correlated with the BV_{rest}, no significant correlations were found.

ΔSV vs. BV

While we found a negative correlation between the changes from SV_{rest} to 40 % $\dot{V}O_{2max}$ ($\Delta SV_{R-40\%}$) and the absolute BV_{rest} (r = −0.40, p = 0.05), the correlation between $\Delta SV_{40–80\%}$ and the absolute $BV_{40\%}$ was positively significant (r = 0.45, p < 0.05, Figure 6).

ΔSV vs. ΔBV

No correlation exists between the changes in SV and the exercise-induced BV shifts (e.g., $\Delta SV_{40–60\%}$ vs. $\Delta BV_{40–60\%}$) at the specific exercise intensities. The same also applies to the values related to BSA.

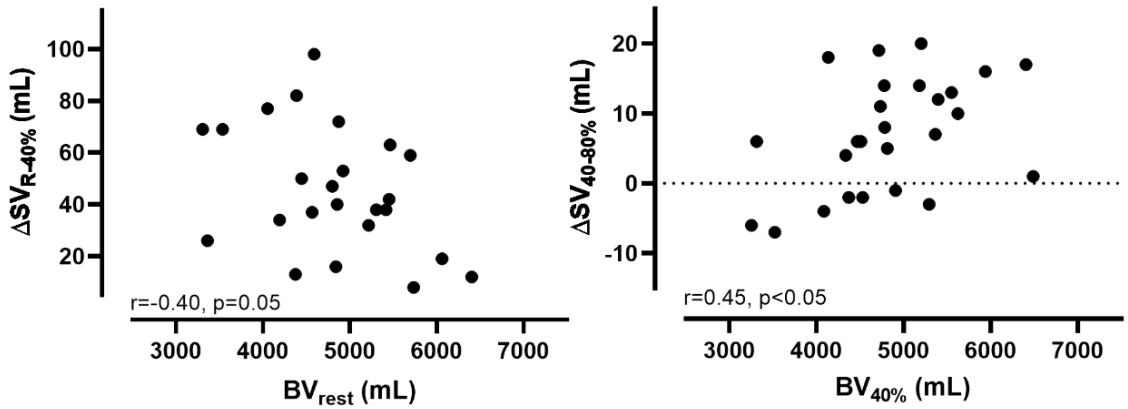

Abbildung 6. Correlations (r) and levels of significance (p) between the changes in stroke volume (ΔSV) and blood volume (ΔBV) from rest to 40 % $\dot{V}O_{2max}$ and from 40 % $\dot{V}O_{2max}$ to 80 % $\dot{V}O_{2max}$.

SV vs. cardiac dimensions

SV_{rest} was also significantly correlated to the LVMM ($r = 0.52$, $p < 0.01$) and LVEDD ($r = 0.41$, $p < 0.05$), respectively. When the LVMM and LVEDD were correlated to the SV at the other exercise intensities, the results were still significant (Table 8). We also found significant correlations between the SV_{max} and LVEDD ($r = 0.70$, $p < 0.001$) and LVMM ($r = 0.68$, $p < 0.001$, see Table 8), respectively.

ΔSV vs. cardiac dimensions

The absolute and relative $\Delta SV_{R\text{-}40\%}$ and $\Delta SV_{40–80\%}$ were both not correlated to the LVMM and LVEDD, respectively. The correlations between $\Delta SV_{60–80\%}$ or $\Delta SV_{60–100\%}$ and the LVMM and LVEDD were also not significant.

Calculated dependencies between $\dot{V}O_{2max}$, $\dot{Q}$ and BV

The slope for an increase in $\dot{Q}$ for every 1 $L \cdot min^{-1}$ increase in $\dot{V}O_{2max}$ was ~5.6 $L \cdot min^{-1}$ ($y = 5.59x + 6.05$). The slope of the respective regression line indicates that a 1 L higher $\dot{Q}_{max}$ was associated with a higher $\dot{V}O_{2max}$ of 104 $mL \cdot min^{-1}$. A 1 L higher $BV_{100\%}$ was associated with a higher $\dot{V}O_{2max}$ of 625 $mL \cdot min^{-1}$. According to the respective regression equation derived from the calculations in the Supplementary Material, a 1 L higher $BV_{100\%}$ was associated with a higher SV_{max} of 16.2 mL. Concerning the significant relationship between $BV_{100\%}$ and $\dot{Q}_{max}$, a 1 L higher $BV_{100\%}$ was associated with a higher $\dot{Q}_{max}$ of 2.5 $L \cdot min^{-1}$. Applying these cross-sectional data to the intra-individual changes in BV during exercise, the 5.7 % reduction in BV found in this study would lead to a decrease in $\dot{Q}_{max}$ and $\dot{V}O_{2max}$ by 627 $mL \cdot min^{-1}$ and 156 $mL \cdot min^{-1}$, respectively. When the abovementioned variables were normalized to body mass and body surface area, the correlations were still significant (see Figure 7).

Tabelle 8. Correlations (r) and levels of significance (p) between the absolute and relative values of SV, BV and cardiac dimensions.

Variable A	**Variable B**	**Absolute**		**Relative** ($\cdot kg^{-1}$)		**Relative** ($\cdot k^{-0.73}$ /$\cdot m^{-2}$)	
		r	*p*	*r*	*p*	*r*	*p*
SV_{max} (mL)	LVEDD (mm)	0.70	<0.001	0.63	0.001	0.52	<0.01
	LVMM (g)	0.68	<0.001	0.56	<0.01	0.52	<0.01
LVEDV (mL)	BV_{rest} (mL)	0.69	<0.001	0.58	<0.01	0.59	<0.01
	$BV_{100\%}$ (mL)	0.65	<0.001	0.51	0.01	0.52	<0.01
LVEDD (mm)	BV_{rest} (mL)	0.60	<0.01	0.23	0.28	0.19	0.37
	$BV_{100\%}$ (mL)	0.62	<0.01	0.30	0.20	0.23	0.27
	$SV_{40\%}$	0.48	<0.05	0.63	0.001	0.44	<0.05
	$SV_{60\%}$	0.55	<0.01	0.67	<0.001	0.50	<0.05
	$SV_{80\%}$	0.61	<0.01	0.64	<0.001	0.47	<0.05
	$SV_{100\%}$	0.57	<0.01	0.54	<0.01	0.42	<0.05
LVMM (g)	BV_{rest} (mL)	0.78	<0.0001	0.61	<0.01	0.58	<0.01
	$BV_{100\%}$ (mL)	0.77	<0.0001	0.61	<0.01	0.58	<0.01
	$SV_{40\%}$	0.51	<0.05	0.52	<0.01	0.45	<0.05
	$SV_{60\%}$	0.57	<0.01	0.58	<0.01	0.52	<0.01
	$SV_{80\%}$	0.68	<0.001	0.61	<0.01	0.58	<0.01
	$SV_{100\%}$	0.51	0.01	0.47	<0.05	0.42	0.05

Data are related to body mass and body surface area. $SV_{40\%}$=stroke volume at 40 % $\dot{V}O_{2max}$, $SV_{60\%}$=stroke volume at 60 % $\dot{V}O_{2max}$, $SV_{80\%}$= stroke volume at 80 % $\dot{V}O_{2max}$, $SV_{100\%}$= stroke volume at $\dot{V}O_{2max}$, SV_{max}=maximum stroke volume, BV_{rest}=blood volume at rest, $BV_{100\%}$=blood volume at $\dot{V}O_{2max}$, LVEDV=left ventricular end-diastolic volume, LVEDD=left ventricular end-diastolic diameter, LVMM=left ventricular muscle mass.

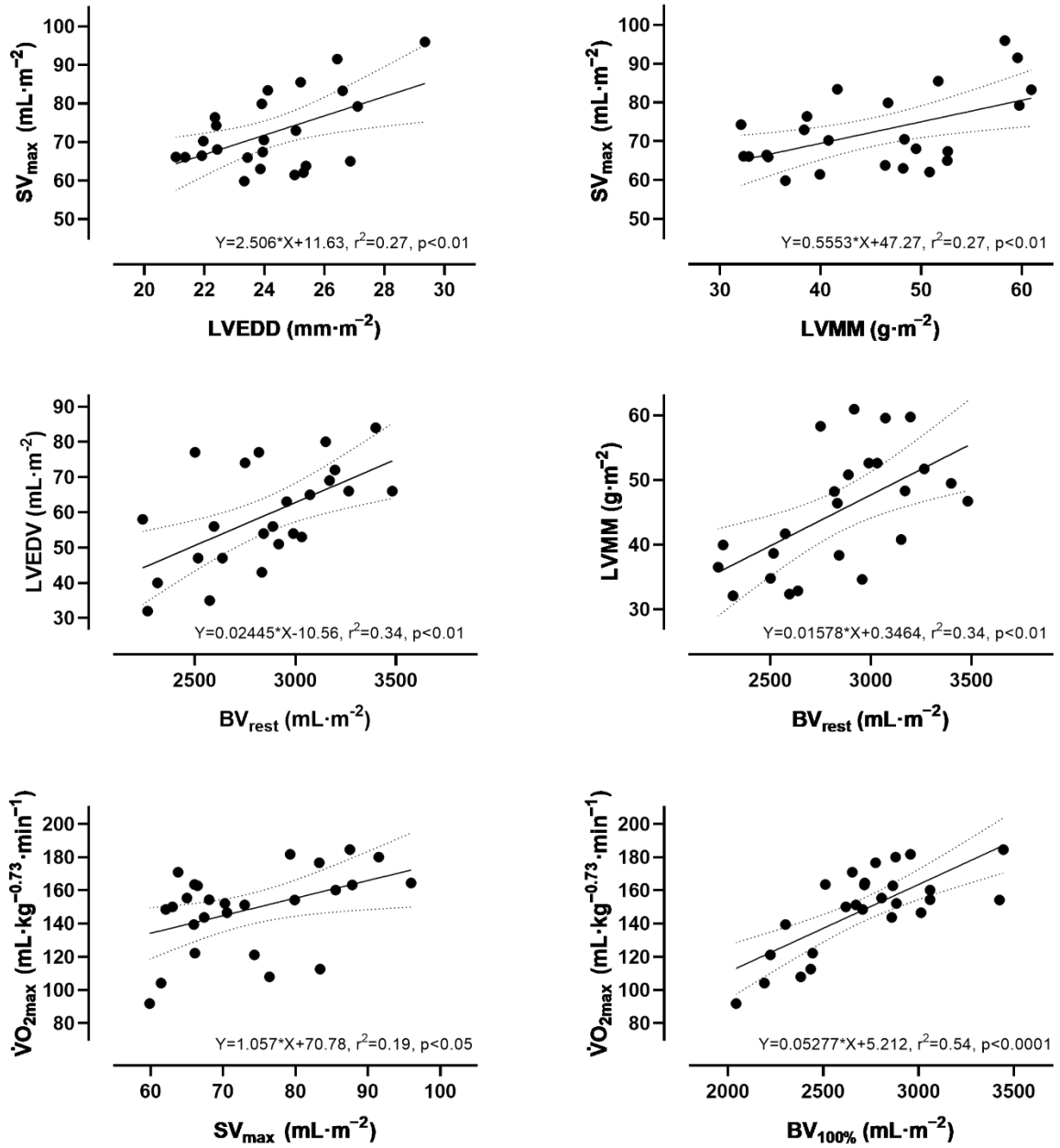

Abbildung 7. Simple linear regression analysis between absolute and relative values of stroke volume, blood volume, cardiac dimensions and maximum.

Discussion and Conclusion

This is one of the few studies that continuously measured SV throughout incremental cycle exercise and, to the best of our knowledge, the first that included continuous BV measurements and correlated them to SV over the entire course of exercise. Our most important findings are that the mean SV response to dynamic cycle ergometer exercise does not seem to plateau in females with heterogeneous endurance capacities. The SV was significantly correlated to the BV at all exercise intensities, except $BV_{40\%}$. Individuals with the highest BVrest showed the smallest changes in SV from rest to 40 %, but the largest from submaximal intensities to $\dot{V}O_{2max}$. Basic resting cardiac dimensions were significantly correlated to the SV at all exercise intensities, but not to the changes in SV. The exercise-induced BV shifts were also not correlated to the changes in SV between the respective exercise intensities, however, they led to a higher oxygen transport capacity via an increase in [Hb].

Stroke volume response

The mean values for SV_{max} in this study are similar to previous reports from moderately trained females *(129,132,146)*, but smaller than in highly endurance trained females *(147)* and both endurance-trained *(129)* and untrained males *(133)*. However, due to the methodology of continuous impedance cardiography and the resulting multiple measurement points, this study may provide further information. First, we identified all previously postulated SV responses to dynamic exercise *(19)*, which include progressive increases (n = 8), plateaus with (n = 4) and without a secondary increase (n = 6) as well as plateaus with a drop (n = 4). Additionally, we observed what was a progressive increase until 80 % $\dot{V}O_{2max}$ followed by a slight drop in SV (n = 4, Figure 5 A). Second, in this female population the SV response did not plateau at submaximal work rates but demonstrated a significant mean increase from 40 % to 80 % $\dot{V}O_{2max}$.

In the literature, there is still disagreement about the course of the SV response in healthy humans as they approach volitional exhaustion *(21,22)*. However, it must be noted that the magnitude of the experimentally determined SV and thus $\dot{Q}$ depends in general on both biological and methodological factors. Concerning the biological factors, previous studies have demonstrated that the SV may decrease at the end of an exhaustive test at least in untrained subjects *(21)* which was explained by the regulatory limit of the heart. In contrast, it has also been demonstrated that especially in endurance-trained athletes, the SV does not plateau during exercise and that the additional increase was mainly attributed to enhanced diastolic function *(131,148)*. Even though we found a significant mean SV increase until 80 % $\dot{V}O_{2max}$, the SV did in fact remain unchanged until exhaustion. Therefore, our results indicate that although no

plateau was reached, the SV did not progressively increase until maximal effort, albeit no drop at exhaustion was discernible. With regard to the methodological approach, it has been stated previously that the quantification of $\dot{Q}$ also considerably depends on the applied method. For instance, in our recent study with males where we found a plateau in SV from submaximal to maximal power outputs *(133)*, we used an inert gas rebreathing method, whereas in this study an impedance cardiography was used. It is postulated that the first tends to underestimate $\dot{Q}$ because of the recirculation of N_2O which depends on the rebreathing time and exercise intensity *(64)*, whereas the PhysioFlow is assumed to overestimate SV especially when thoracic blood volume decreases rapidly *(149,150)*, although that does not seem to be a consistent finding *(70,71)*. In fact, studies reporting progressive increases throughout dynamic exercise mostly used an impedance cardiography method *(149)*. However, we found a similar slope for an increase in $\dot{Q}$ per 1 $L \cdot min^{-1}$ increase in $\dot{V}O_2$ (~5.6 $L \cdot min^{-1}$) using the PhysioFlow impedance cardiography as was reported in previous invasive investigations *(66,72,73)*. Therefore, we can assume that our data are valid and physiological conclusions can be drawn for the interpretation of the SV course, even though we did not perform multiple measurements to confirm consistent intra-individual SV profiles. The interpretation of the SV course and its comparison with the scientific literature must always include both biological and methodological factors, as we believe that a large proportion of the sometimes-contradictory results may be due to different methodological approaches.

Stroke volume and blood volume

In this study, we found significant correlations between the SV and BV at each of the exercise intensities, except for 40 % $\dot{V}O_{2max}$ (see Supplementary Material). Furthermore, the correlations became even stronger with increasing exercise intensity. Our data also demonstrate that the smaller the BV_{rest}, the higher the first increase in SV until 40 % $\dot{V}O_{2max}$, as we found a trend towards a negative correlation between $\Delta SV_{R\text{-}40\%}$ and BV_{rest}. This is also supported by the interindividual differences in the $\Delta SV_{R\text{-}40\%}$ ranging from 8 to 98 mL indicating that in individuals with both a high BV_{rest} and SV_{rest} the hemodynamic output changes only to limited extent whereas individuals with a low BV_{rest} and SV_{rest} have to mobilize a higher percentage of their BV in order to meet their metabolic demand. In other words, it is likely that a larger BV_{rest} is associated with a larger central BV and therefore greater cardiac filling during diastole leading to a larger SV_{rest}. In contrast, for a lower BV_{rest} and thus central BV there is more potential for an increase in cardiac filling and thus SV_{rest} due to peripheral volume shifts at the onset of

exercise. As expected, the correlation is reversed in the further course of the exercise and becomes significant ($\Delta SV_{40–80\%}$ vs. BV_{rest}, $r = 0.45$, $p < 0.05$). This might indicate that only individuals with an initially high BV are able to further increase SV at higher exercise intensities. Previous investigations have repeatedly demonstrated that a large BV is a prerequisite that allows for a larger SV during exercise due to an increase in central venous pressure and an elevated venous return *(76,78,135,151,152)*. This augments atrial and ventricular preload, which in turn enhances ventricular filling and results in an increased response of the Frank-Starling mechanism of the left ventricle *(132)*.

At lower absolute oxygen uptake values the variability in SV was large which is most likely due to the heterogeneous endurance capacities of our participants. This would mean, that a given $\dot{Q}$ could either be facilitated via a larger SV or HR. Therefore, a high BV would be less important for SV at submaximal intensities, which is supported by the non-existent correlation between the BV and the SV at the same absolute submaximal $\dot{V}O_{2max}$. However, it must be stated that at any intensity a high BV is generally beneficial for exercise performance as it allows for better thermoregulation *(2)* or an improved lactate distribution *(153)*. At high oxygen uptake values, however, the variability in SV becomes smaller, which might be due to the fact, that for achieving such high $\dot{V}O_{2max}$, the SV becomes the limiting determinant, thus leading to converging high SV values (see Figure 5 B).

In the context of the exercise-induced BV shifts, it remains uncertain if they might actually impair the SV course during dynamic exercise. While we found a linear decrease in BV, the SV in fact progressively increased until 80 % $\dot{V}O_{2max}$. In addition, we found no correlation between the changes in SV (ΔSV) and the exercise-induced BV shifts (ΔBV) between any exercise intensity. It is therefore reasonable to assume that the volume shifts are fully compensated and even outmatched by an increased venous return *(128)*. Nevertheless, the BV shifts may lead to SV_{max} and $\dot{Q}_{max}$ values that are possibly below the values, that would have been expected had no fluid been shifted. In this context it would be of great interest if volume matched fluid compensation during dynamic exercise in the extent of the individual volume shifts, e.g., via plasma or dextran infusion, would lead to a greater increase in SV and thus $\dot{Q}$.

Stroke volume and cardiac dimensions

It is generally accepted, that there is also a close relationship between the SV and the cardiac dimensions *(154)*. We hereby confirm this relationship based on the significant correlation between the SV_{rest}/SV_{max} and the LVMM and LVEDD. Additionally, we can also provide data for the submaximal intensities with the important limitation that only cardiac data at rest were

available. Our data clearly demonstrate that throughout the exercise period, the SV is significantly correlated to the cardiac dimensions. This is in line with the general conviction, that larger cardiac dimensions are necessary to achieve higher SV values during dynamic exercise *(155–157)*. In this study we also found significant correlations between the relative SV and cardiac dimensions indicating that when removing the influence of body size, the independent impact of other factors, e.g., training status, becomes apparent.

In contrast to the BV, we found no correlation between the cardiac dimensions and changes in SV (ΔSV) throughout the exercise period. It can be concluded, that the sole consideration of the resting cardiac dimensions cannot explain the variation in SV and that additional factors, e.g., cardiac compliance or left-ventricular contractility also impact the behaviour of the SV during dynamic exercise *(85)*. In general, our findings indicate that both the Frank-Starling mechanism and probably left ventricular function exert a substantial influence on the SV throughout exercise *(132)*, even though we did not perform a strain imaging.

Blood volume and cardiac dimensions

Since we and others have demonstrated that both the BV and cardiac dimensions determine the SV response to dynamic exercise, it is reasonable to assume that both parameters also influence each other. We were recently able to demonstrate that in males with heterogeneous endurance capacities there was a significant correlation between the BV and the resting cardiac dimensions, as was also found in this study. Higher BV typically result in an increased venous return and cardiac preload, thus serving for a potential stimulus for cardiac remodelling, e.g., after long-term endurance training *(158)*.

The connection between the BV and cardiac dimensions obtained from cross-sectional studies was also demonstrated when untrained subjects were matched to trained endurance athletes in terms of BV via dextran infusion, which led to an increase in SV in the untrained group. However, these values were still lower than those in the trained athletes *(79)*, which demonstrates that the BV alone cannot explain the differences in SV. Therefore, enhanced cardiac dimensions, cardiac contractility and/or other mechanisms, e.g., the ratio between hemodynamic active and inactive BV *(78)* may attribute to the SV response along with a larger BV.

Fluid shifts and oxygen transport

Percentage changes in BV were calculated previously based on changes in [Hb] and Hct *(110)*, but there are few studies available on absolute volume reductions during dynamic exercise.

While we were recently able to demonstrate an 8 % (~550 mL) decrease in men with heterogeneous endurance capacities *(133)*, the female cohort in this study exhibited both a smaller relative and absolute volume reduction (~6 %, 280 mL). Other studies also demonstrated larger changes in BV in men when compared to the females in this study *(36,82)*. These sex-specific differences are most likely due to the smaller active muscle mass during dynamic exercise in women *(81)* whereas the fluid shifts are generally the result of a greater filtration rate caused by an increase in blood pressure, sweat loss and especially lactate accumulation and the breakdown of creatine phosphate within the muscle cell *(38)*. The latter of which causes an increased osmotic gradient that, in turn, leads to an influx of water into the intracellular and interstitial space *(41,42)*. Although we recognized a trend between $\Delta BV_{R\text{-}100\%}$ and BV_{rest} ($r = 0.38$, $p = 0.06$), no correlation was found between the $\Delta BV_{R\text{-}100\%}$ and the maximum lactate concentrations or $\dot{V}O_{2max}$, respectively. Therefore, it remains uncertain if endurance trained athletes shift more water into the intracellular space during incremental exercise.

In the context of the oxygen transport capacity, the volume shifts induced an increase in [Hb] by 0.8 $g \cdot dL^{-1}$ until maximum exercise that would theoretically lead to an increase in CaO_2 by 1.1 $mL \cdot dL^{-1}$. However, due to the simultaneous decrease in ScO_2 by ~4 %, the CaO_2 increased by only 0.4 $mL \cdot dL^{-1}$. In this study population, the increase in [Hb] was lower and the decrease in ScO_{2max} was less pronounced when compared to males *(133)* resulting in a similar increase in CaO_{2max} in both groups. It was previously demonstrated that a high $\dot{Q}_{max}$ may shorten the time for alveolar and capillary gas equilibration at the lungs which leads to an exercise-induced arterial hypoxemia that would reduce CaO_2 *(75)*. Since we found no correlation between $\dot{Q}_{max}$ and ScO_{2max}, we hypothesize that the women's $\dot{Q}_{max}$ values are too small to induce such a desaturation level. Our results clearly suggest that the BV shifts influence both oxygen transport capacity and $\dot{Q}$. When comparing the calculated amount of oxygen transported in the arterial system either with or without the effects of the fluid shifts on [Hb] and $\dot{Q}_{max}$ the result is 4.314 $mL \cdot min^{-1}$ and 4.153 $mL \cdot min^{-1}$, respectively. This demonstrates that the fluid shifts more than compensate for the decrease in ScO_2 and, if applicable, $\dot{Q}_{max}$. Like acute altitude effects, the hemoconcentration due to transient plasma volume shifts could, therefore, be interpreted as a physiological adjustment to maintain and in this case even improve oxygen transport capacity without compromising performance *(84)*.

$\dot{V}O_{2max}$

The $\dot{V}O_{2max}$ is calculated on the basis of the Fick principle and therefore depends on several anatomical and physiological parameters *(5)*. We found the strongest correlation between the

$\dot{V}O_{2max}$ and BV_{max} and Hbmass, respectively (see Supplementary Material). As derived from the respective regression equation, a 1 L higher BV was associated with a higher $\dot{V}O_{2max}$ by 625 mL·min^{-1}. As we have already mentioned, the BV exerts a substantial influence on both the SV and the cardiac dimensions, whereas the Hbmass exerts a substantial influence on the oxygen transport capacity and $avDO_{2max}$.

Even though the results from the cross-sectional study must be interpreted with caution, the possible influence of the exercise-induced BV shifts on the SV and the $\dot{V}O_{2max}$ can be estimated. Our results showed that a 1 L higher $BV_{100\%}$ was associated with a higher SV_{max} of approximately 16.2 mL, leading to a higher $\dot{Q}_{max}$ of approximately 2.5 L·min^{-1}. As the BV significantly decreased from rest to maximal exercise by 280 mL (5.7 %), we calculate a possible decrease in SV_{max} by 4.5 mL and in $\dot{Q}_{max}$ by 627 mL·min^{-1}. As a consequence, without the compensation via the increase in CaO_2 due to the change in [Hb], the $\dot{V}O_{2max}$ would also be reduced by 156 mL·min^{-1}, which closely mirrors experimental data reporting a decrease by 125 mL·min^{-1} immediately after a blood volume reduction to a similar extent *(83)*.

Limitations

There are several limitations to this study. It is well known that the determination of $\dot{Q}$ during exercise depends significantly on the applied method. The PhysioFlow impedance cardiography is assumed to be affected by movement under strenuous exercise, respiratory artefacts and possibly accumulation of fluid in the lungs which was associated with a high intersubject variance in previous studies*(66,159,160)*. This must be considered when interpreting the results of this study and comparing them with previous investigations. However, it is validated against the direct Fick method during exercise in healthy subjects *(70)* and its major advantage is in the continuous hemodynamic monitoring that allows a more comprehensive evaluation of the SV response. Additionally, the regression equation we calculated from the results in this study ($\dot{Q}$ = 5.59 x $\dot{V}O_{2max}$ + 6.05) is well in line with previous invasively measured data *(72,73)*, which is a strong indication for the validity of the PhysioFlow, even though we did not perform multiple measurements to confirm consistent intra-individual SV profiles.

We have recruited a healthy population with heterogenous endurance capacities including sedentary, moderately and highly endurance trained participants to calculate correlations with an expected larger scattering of anatomical and physiological characteristics. For this reason, however, we did not have a sufficient number of participants in each of the aforementioned subpopulations and thus refrained from any statistical group analysis. We conducted correlation and

linear regression analyses, thus we cannot confirm cause and effect. The quantitative dependencies that we drew from our analyses must therefore be interpreted with caution and are likely multifactorially driven. For the calculation of the possible influence of the BV changes on the SV course during dynamic exercise, we use data from the regression analyses, however, direct manipulations of BV must be applied to compare the effects of the volume shifts on hemodynamic mechanisms. Sweat loss estimates or direct measures of sweat loss should also be collected as they could impact the PV reductions during the incremental cycle ergometer exercise. To answer whether the increase in hemoconcentration and consequently the elevated CaO_2 really are fully compensatory for the reductions in $\dot{Q}_{max}$ discussed here, additional data such as blood flow to working muscle, mean arterial pressure and vascular resistance should also be collected. Moreover, the present study cannot explain whether the increased CaO_2 influences a regulatory feedback mechanism on the $\dot{Q}_{max}$ *(109)*.

Conclusion

In 60 % of our female participants with heterogeneous endurance capacities the SV does not plateau but progressively increases throughout incremental work until 80 % $\dot{V}O_{2max}$. The BV does not seem to be relevant for the initial rise in SV but rather for increasing SV beyond submaximal exercise intensities. At all exercise intensities the SV was significantly correlated to the resting cardiac dimensions, which might be the result of adaptations to an increased volume load. The exercise-induced BV shifts may have a detrimental effect on the SV and $\dot{V}O_{2max}$, however, their negative effect on $\dot{V}O_{2max}$ is completely compensated for due to the increase in [Hb] and therefore arterial oxygen content.

8 Artikel III: Relationship between Blood Volume, Blood Lactate Quantity and Lactate Concentrations during Exercise

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Abstract

We wanted to determine the influence of total blood volume (BV) and blood lactate quantity on lactate concentrations during incremental exercise. Twenty-six healthy, nonsmoking, heterogeneously trained females (27.5 ± 5.9 ys) performed an incremental cardiopulmonary exercise test on a cycle ergometer during which maximum oxygen uptake ($\dot{V}O_{2max}$), lactate concentrations ([La^-]) and hemoglobin concentrations ([Hb]) were determined. Hemoglobin mass and blood volume (BV) were determined using an optimised carbon monoxide-rebreathing method. $\dot{V}O_{2max}$ and maximum power (P_{max}) ranged between 32 and 62 $mL \cdot min^{-1} \cdot kg^{-1}$ and 2.3 and 5.5$W \cdot kg^{-1}$, respectively. BV ranged between 81 and 121 $mL \cdot kg^{-1}$ of lean body mass and decreased by 280 ± 115 mL (5.7 %, $p = 0.001$) until P_{max}. At P_{max}, the [La^-] was significantly correlated to the systemic lactate quantity (La^-, $r = 0.84$, $p < 0.0001$) but also significantly negatively correlated to the BV ($r = -0.44$, $p < 0.05$). We calculated that the exercise-induced BV shifts significantly reduced the lactate transport capacity by 10.8 % ($p < 0.0001$). Our results demonstrate that both the total BV and La^- have a major influence on the resulting [La^-] during dynamic exercise. Moreover, the blood La^- transport capacity might be significantly reduced by the shift in plasma volume. We conclude, that the total BV might be another relevant factor in the interpretation of [La^-] during a cardio-pulmonary exercise test.

Keywords: lactate kinetics; hemoglobin concentration; hematocrit; plasma volume; erythrocyte volume; performance diagnostics

Introduction

Lactate is now recognised as a major metabolic intermediate and signalling molecule that is used for oxidative energy supply and is transported between different cells, tissues, and organs by means of transport proteins *(161–167)*. Lactate is widely accepted as a diagnostical marker and lactate kinetics or lactate concentrations ([La^-] are commonly used in the field of sports medicine for the assessment of endurance performance, e.g., during an incremental cardiopulmonary exercise (CPX) test *(48)*. Moreover, exercise prescriptions based on [La^-] allow for precise and predictable regulation of acute metabolic and cardiorespiratory responses during dynamic exercise, as is reflected in the previously postulated lactate turn point model *(48,49)*.

However, [La^-] must always be considered in light of the prevailing production and elimination rates and numerous studies have shown that there are several factors that can significantly influence these rates leading to highly variable results. These include, for example, the applied protocol or workload characteristics *(168–170)* of a CPX test, the previous diet in relation to muscle glycogen *(171–174)*, muscle fibre-type composition *(175–177)*, the source of blood sampling *(170,178,179)*, or cerebral lactate uptake *(180)*.

Another important factor that has not yet been considered in this context may be the total blood volume (BV). This is surprising since the BV not only serves as a distribution medium but also transports lactate to other cells and organs for the oxidative energy supply or gluconeogenetic metabolism. It can be assumed that the concentration of any substance dissolved in a medium is dependent on both the size of the medium and the amount of substance dissolved in the medium. Usually, [La^-] is measured throughout an exercise test regardless of the medium, in this case, total BV. It is well known, however, that total BV not only differs greatly between individuals, e.g., due to training-induced volume expansion or a genetic predisposition *(3,78,181)* but also decreases by up to 10 % during dynamic exercise mainly as a result of plasma volume (PV) shifts *(36,133)*. With respect to the latter, Davies et al. previously concluded that [La^-] above the lactate threshold should be corrected for this decrease in PV *(37)*. Moreover, since significantly more lactate is transported in the plasma than in the erythrocytes, especially during intensive exercise *(182)*, PV losses might also have a considerably negative impact on the lactate transport capacity. Consequently, the total BV may have an impact on both inter- and intra-individual comparisons of [La^-]. Therefore, we hypothesise that the larger (or the smaller) the total BV, the lower (or the higher) the [La^-] tends to be in the course of an incremental ergometer test. In addition, if the BV is known, it is also possible to calculate the absolute lactate quantity (La^-) and thus, its impact on [La^-]. To the best of our knowledge, this has not yet been

done. Therefore, the aim of this study was to determine the total BV and La^- during an incremental CPX test on a cycle ergometer in healthy volunteers with heterogenous endurance capacities and quantify their influence on the measured [La^-] during dynamic exercise.

Methods

Participants

This was a secondary outcome analysis of a previously published descriptive cross-sectional study *(183)* that reports preliminary observations. Twenty-six healthy, nonsmoking females with heterogenous endurance capacity and no history of cardiac disease were included in the study (see Table 10 for participant characteristics). The participants provided written consent after being informed of the study design, the associated risks, and their right to withdraw at any time. The study was conducted in conformity with the declaration of Helsinki and Good Clinical Practice and the study protocol was approved by the ethics committee of the University of Bayreuth in Germany (O 1305/1–GB).

Tabelle 9. Participant characteristics (n = 26).

	Mean ± SD	**Min**	**Max**	**95 % CI**
Age (y)	27.5 ± 5.9	19	40	25.1 - 29.9
Height (cm)	167.7 ± 6.5	154	180	165 - 170
Body mass (kg)	60.1 ± 7.0	47.5	73.5	58.1 - 63.9
Body mass index ($kg \cdot m^{-2}$)	21.6 ± 1.6	18.6	25.1	20.9 - 22.3
Lean body mass (kg)	47.4 ± 5.9	35.9	56.9	44.9 - 49.9
Fat mass (%)	22.2 ± 5.6	9.4	35.0	19.8 - 24.6
Ferritin ($\mu g \cdot L^{-1}$)	44 ± 24	16	105	34.2 - 54.0
C-reactive protein ($mg \cdot dL^{-1}$)	1.37 ± 1.26	0.3	4.9	1.43 - 2.52
$\dot{V}O_{2max}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	49.0 ± 8.1	31.8	61.7	45.7 - 52.3
P_{max} ($W \cdot kg^{-1}$)	4.2 ± 0.8	117	334	236 - 282
Hbmass ($g \cdot kg^{-1}$)	9.8 ± 1.2	7.8	12.7	9.3 - 10.3

The data are presented as the mean values ± standard deviations. Min = minimum, Max = maximum, CI = confidence interval.

Study design

After anthropometric measurements including analysis of body composition using a bioelectrical impedance analysis were conducted, a cubital venous blood sample was drawn for a full blood count as well as ferritin concentrations to exclude any iron deficiencies. The participants then performed an incremental CPX test on a cycle ergometer to determine the maximum power (P_{max}) and maximum oxygen uptake ($\dot{V}O_{2max}$). During this test, the hemoglobin concentration ([Hb]) for the calculation of BV and capillary lactate concentrations ([La^-]) were determined.

The hemoglobin mass (Hbmass) was measured twice on consecutive days and within 7 days after the ergometer test using a CO-rebreathing method. The BV at rest and during exercise was calculated subsequently based on the Hbmass and [Hb].

Anthropometry and Blood Sampling

Prior to the exercise test, lean body mass (LBM) and fat mass were measured twice consecutively using a bioelectrical impedance analyser (InBody 720, InBody Co., Seoul, Republic of Korea). Cubital venous blood samples (8 mL) were drawn after the participants rested for 15 min in an upright seated position. Heparinised blood samples were analysed using a fully automated haematology system (Sysmex XN 1000-1-A, Sysmex, Norderstedt, Germany) for red blood cells including hemoglobin concentration ([Hb]) and hematocrit (Hct). The serum ferritin and C-reactive protein (CRP) concentrations were determined by enzyme immunoassays [ferritin: LKFE1, CRP: highly sensitive—LKCRP1; ELISA & Immulite 1000 (Siemens Healthcare Diagnostics GmbH, Erlangen, Germany)].

Cardio-Pulmonary Exercise Test and Blood Sampling

Pmax was determined using an incremental protocol on a cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands). After a 3-min warm-up phase of 50 W, the mechanical power was increased by 50 Watts every 3 min (stepwise by 17, 17, and 16 Watts per minute) until subject exhaustion was reached. The $\dot{V}O_2$ was determined via breath-by-breath technology (Metalyzer 3B, Cortex, Leipzig, Germany), and the $\dot{V}O_{2max}$) was calculated as the highest 30 s interval before exhaustion. Capillary blood samples were taken from a hyperemized earlobe before exercise, every 3 min during exercise, and immediately at exhaustion to determine the [Hb] using a calibrated photometric analysis (HemoCue 201, HemoCue AB, Ängelholm, Sweden). At the same time points, capillary blood samples (20 L) were taken from the other earlobe to measure the [La^-] using an enzymatic-amperometric approach (Biosen S-Line, EKF-Diagnostic, Barleben, Germany). Further blood samples for the determination of [La^-] were taken 1-, 3-, 5- and 7-min post-exercise. The maximum lactate concentration was defined as [La^-]max. The absolute lactate quantity (La^-) in mmol at the respective intensities was calculated as the product of [La^-] and BV and indexed for lean body mass. The [La^- and La^- at 60 % of P_{max} ($P_{60\%}$) and at P_{max} were defined as $[La^-]_{60\%}$ and $La^-_{60\%}$ and $[La^-]_{end}$ and La^-_{end}, respectively. The lactate transport capacity in the erythrocyte and in the plasma volume (PV) was calculated based on the blood volume at P_{max} (BV_{end}), the Hct_{end}, and the corresponding [La^-]. Additionally, the [La^-] and La^- in the PV and the erythrocyte volume (ECV) at P_{max} were separately estimated assuming a [La^-] ratio of 1:0.3 between the PV and the ECV *(182)*.

Determination of Hemoglobin Mass and Blood Volume

The Hbmass, BV, PV, and ECV were determined using a carbon monoxide (CO)-rebreathing procedure according to methods described in previous investigations *(50,51,114)*. In brief, an individual dose of CO (0.8–0.9 $mL \cdot kg^{-1}$, CO 3.7, Linde AG, Unterschleißheim, Germany) was administered and rebreathed along with 3 L of pure medical oxygen (Med. O_2 UN 1072, Rießner-Gase GmbH, Lichtenfels, Germany) for 2 min. Capillary blood samples were taken before and 6 and 8 min post administration of the CO dose. The blood samples were measured for the determination of %HbCO using an OSM III hemoximeter (Radiometer, Copenhagen, Denmark). The Hbmass was calculated based on the mean change in %HbCO before and after the CO was rebreathed. As part of the equation to calculate changes in BV during the exercise period, the capillary [Hb] was converted to the venous conditions *(115,117)*. The Hct_{end} was calculated as the quotient of $[Hb]_{end}$ and the mean corpuscular hemoglobin concentration (MCHC) at rest *(184)*. The BV was calculated according to the following formula where 0.91 = cell factor at sea level *(52)*:

$$BV\ (mL) = Hbmass\ (g) \times 100 \div [Hb]\ (g \cdot \mathrm{dL}^{-1}) \times 0.91^{-1} \quad (1)$$

The BV at rest and at $P_{60\%}$ were defined as BV_{rest} and $BV_{60\%}$, respectively. The BV at maximum power was defined as BV_{end}. For the calculation of the $BV_{60\%}$, the [Hb], which was determined at rest and every 3 min during exercise, was interpolated for the respective exercise intensity, if necessary. Hbmass was measured twice on consecutive days and within 7 days after the ergometer test with a possible first test at least 2 h after the CPX test when the plasma volumes had returned to pre-exercise values *(113)*. Since the Hbmass does not change over short periods *(56)*, the temporary offset determination of the [Hb] for the calculation of the BV is possible without compromising accuracy. For a detailed description and the accuracy of the methods see *(50,51,114)*. The typical error for Hbmass in our laboratory is 1.5 %, which is comparable to previous investigations *(116,117)*, while the typical error for BV is 2.5 %.

Statistical Analysis

The data are presented as means and standard deviations. Statistical analysis was conducted using GraphPad Prism Version 8.0.2 (GraphPad Software, Inc., San Diego, CA, USA). Testing for normality was performed using the Shapiro-Wilk test. Pearson correlation coefficients or nonparametric Spearman correlations were computed to prove any relationship between the two variables. A paired t-test was computed to calculate the differences in La^- with and without the

BV shifts. Multiple linear regression was performed to predict the value of one dependent variable (e.g., [La^-]) based on two independent variables (e.g., BV and La^-). The level of significance was set to $p \leq 0.05$.

Results

$\dot{V}O_{2max}$ ranged between 32 and 62 $mL \cdot kg^{-1} \cdot min^{-1}$. P_{max} ranged between 2.3 and 5.5 $W \cdot kg^{-1}$. Maximum heart rate ranged between 159–201 beats per minute, and the respiratory exchange ratio at P_{max} ranged between 1.13 and 1.34. The Hbmass ranged between 7.8 and 12.7 $g \cdot kg^{-1}$. The BV_{rest} decreased by 280 ± 115 mL (5.7 %, $p = 0.001$) until P_{max} leading to an increase in [Hb] by 0.8 ± 0.3 $g \cdot dL^{-1}$ ($p < 0.001$). Data on the BV, La^- and [La^-] at submaximal and maximal power can be found in Table 10.

Tabelle 10. Blood lactate and blood volume at rest and during the cardio-pulmonary exercise test.

	Mean ± SD	**Min**	**Max**	**95 % CI**
$[La^-]_{60\%}$ ($mmol \cdot L^{-1}$)	2.5 ± 0.9	1.1	4.5	2.1 - 2.9
$La^-_{60\%}$ (mmol)	11.4 ± 4.2	5.6	20.8	9.6 - 13.1
$La^-_{60\%}$ ($mmol \cdot kg^{-1}$ LBM)	0.11 ± 0.04	0.06	0.22	0.09 - 0.14
$[La^-]_{end}$ ($mmol \cdot L^{-1}$)	11.3 ± 2.2	8.5	17.2	10.3 - 12.1
La^-_{end} (mmol)	52 ± 12.2	28.6	75.3	46.7 - 56.8
La^-_{end} ($mmol \cdot kg^{-1}$ LBM)	1.08 ± 0.19	0.79	1.46	1.01 - 1.16
$[La^-]_{max}$ ($mmol \cdot L^{-1}$)	12.1 ± 2.4	8.5	18.4	11.2 - 13.1
BV_{rest} (mL)	4889 ± 836	3306	6461	4551 - 5227
BV_{rest} ($mL \cdot kg^{-1}$ LBM)	102.0 ± 9.9	81	121	99 - 107
BV_{end} (mL)	4609 ± 799	3063	6298	4286 - 4932
BV_{end} ($mL \cdot kg^{-1}$ LBM)	97.0 ± 9.5	75	116	92 - 100
$[Hb]_{rest}$ ($g \cdot dL^{-1}$)	13.4 ± 0.75	11.5	15.3	13.1 - 13.7
$[Hb]_{end}$ ($g \cdot dL^{-1}$)	14.2 ± 0.78	12.2	16.0	13.9 - 14.5

SD = standard deviation, Min = minimum, Max = maximum, CI = confidence interval of the mean, $[La^-]_{60\%}$ = lactate concentration at $P_{60\%}$, $[La^-]_{end}$ = lactate concentration at maximum exercise, $La^-_{60\%}$ = lactate quantity at $P_{60\%}$, La^-_{end} = lactate quantity at maximum exercise, $[La^-]_{max}$ = maximum lactate concentration, BV_{rest} = blood volume at rest prior to exercise, BV_{end} = blood volume at maximum exercise, LBM = lean body mass, [Hb] = hemoglobin concentration.

As depicted in Figure 9 A, $[La^-]_{end}$ was significantly correlated to La^-_{end} (y = 10.2x + 0.2378, r = 0.84, $p < 0.0001$). However, we found no correlation between the La^-_{end} and BV_{end} (Figure 9 B). In contrast, the $[La^-]_{end}$ was significantly and negatively correlated to BV_{end} (y = −0.104x + 21.34, r = −0.44, $p < 0.05$, Figure 9 C). Similar results were found between $[La^-]_{60\%}$ and $La^-_{60\%}$ (y = 20.2x + 0.139, r = 0.92, $p < 0.0001$), however, the correlation between $[La^-]_{60\%}$ and $BV_{60\%}$ was not significant. As a result of the exercise-induced BV shifts, the $[La^-]_{60\%}$ and $[La^-]_{end}$ were 0.12 ± 0.09 and 0.66 ± 0.29 mmol·L^{-1} higher, respectively, when compared to the theoretical situation had the plasma volume and La^- been unchanged.

The lactate quantity (La^-_{end}) in the total BV at maximum power was 51.8 ± 12.2 mmol. It was 10.8 % lower when compared to the calculated La^-_{end} with unchanged plasma volume and unchanged lactate concentration (56.3 ± 13.6 mmol, $p < 0.0001$, Figure 8). Multiple linear regression revealed that, when indexed for lean body mass, both BV_{end} (β = −0.1244, $p < 0.0001$) and La^-_{end} (β = 10.78, $p < 0.0001$) significantly influence $[La^-]_{end}$. For the submaximal exercise intensity, significant results were only observed for $La^-_{60\%}$ (β = 19.71, $p < 0.0001$).

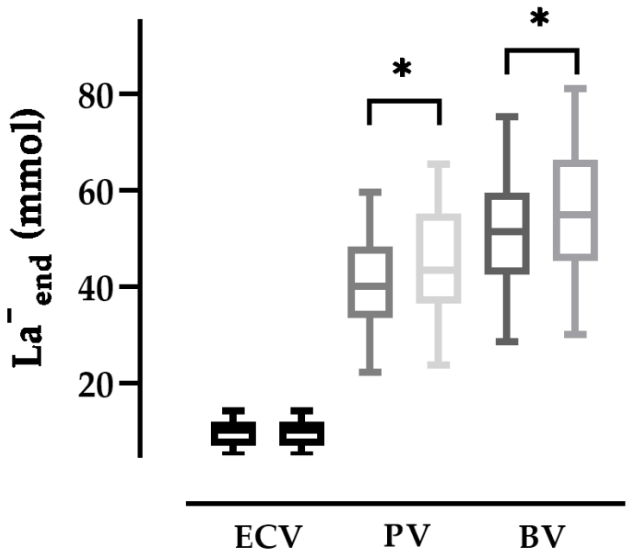

Abbildung 8. Blood lactate quantity at maximum power (La^-_{end}) in the erythrocyte volume (ECV), plasma volume (PV), and total blood volume (BV) with (left) and without (right) blood volume shifts ($p < 0.0001$). La^-_{end} was initially calculated as the product of BV_{end} and $[La^-]_{end}$ (* indicates $p < 0.0001$). The displayed values for La^-_{end} were estimated assuming a $[La^-]$ ratio of 1:0.3 between the plasma and erythrocyte *(182)*.

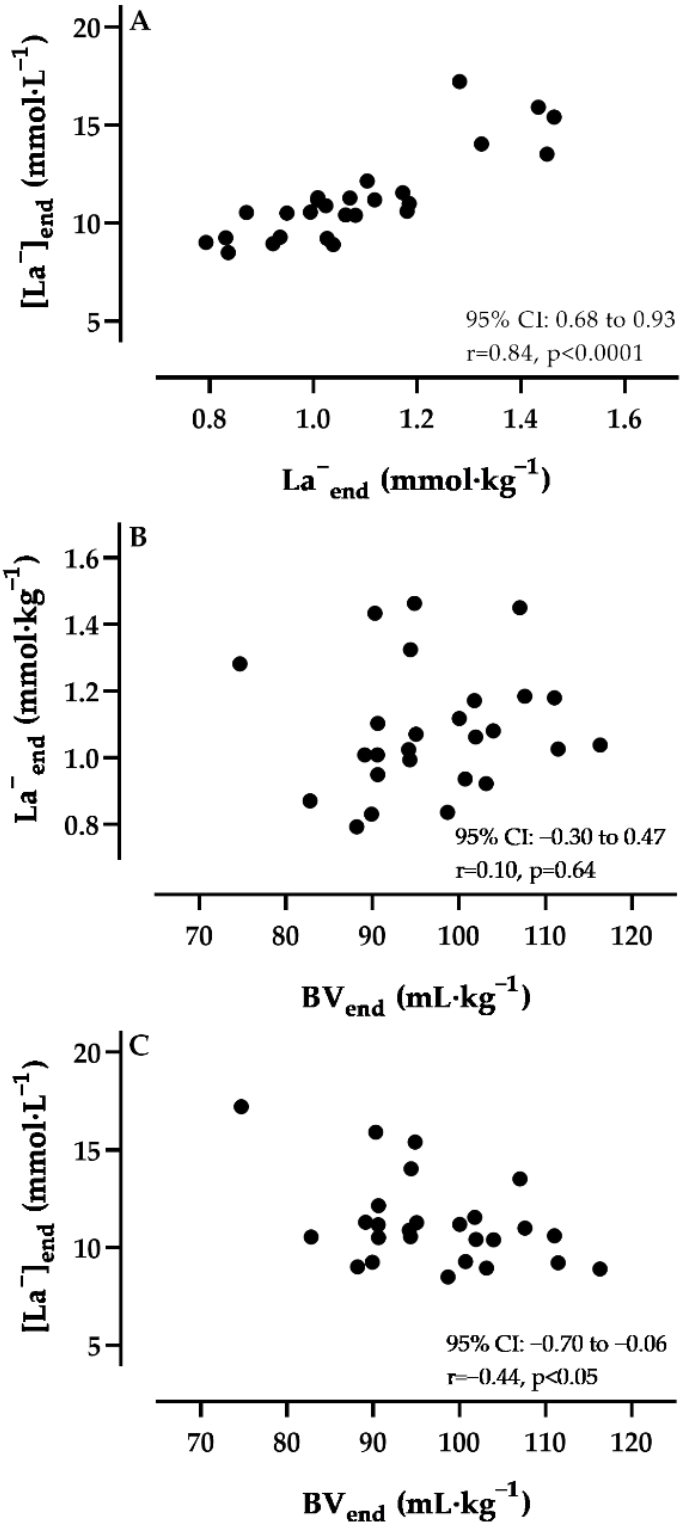

Abbildung 9. Correlation coefficients for the lactate concentrations ($[La^-]_{end}$) and lactate quantity (La^-_{end}) (A), La^-_{end} and blood volume (BV_{end}) (B), and $[La^-]_{end}$ and BV_{end} (C). Data were indexed for lean body mass.

Discussion and Conclusion

This study aimed to calculate the influence of total BV and absolute lactate quantity on the measured [La^-] during an incremental CPX test on a cycle ergometer in healthy volunteers with heterogenous endurance capacities. Our findings confirm the theoretical assumption that both the blood volume and the lactate quantity have an impact on the resulting [La^-]. In addition, the exercise-induced BV shifts led to a significant 10.8 % reduction in the lactate transport capacity.

The measured [La^-] in the blood is generally the result of lactate production (e.g., within the muscle cells) and lactate elimination (e.g., the diffusion of lactate into the PV and its distribution to other cells and organs for lactate clearance). The latter also includes an individual's total BV as a distribution space and the exercise-induced BV shifts. Previous investigations have already dealt in detail with various factors influencing lactate production and elimination rates *(170,171,177,185,186)*, however, to the best of our knowledge, this is the first study that will focus exclusively on the potential role of the BV.

The role of blood volume as distribution space: In theory, if the exchange of lactate between cells remains constant, then a higher BV would consequently lead to lower [La^-] and vice versa. On the other hand, for a given [La^-], a higher La^- would also be associated with a higher BV and vice versa. Our data demonstrate that both assumptions are equally true, however, there are quantitative differences between the two mechanisms.

As demonstrated in the multiple linear regression analysis, both the BV_{end} ($\beta = -0.1244$, $p < 0.0001$) and La^-_{end} ($\beta = 10.78$, $p < 0.0001$) significantly influence the $[La^-]_{end}$. With regard to the correlation between the La^-_{end} and BV_{end} (Figure 9 B), however, no significance was found. This finding might be explained by a plateau in net lactate release at maximum exercise indicating a disturbance in lactate exchangeability *(187–189)*. In contrast, the larger lactate quantity is not sufficient to align the [La^-_{end}] with different BV, which is confirmed by the significant negative correlation between $[La^-]_{end}$ and BV_{end} (Figure 9 C). Therefore, a higher BV might have two opposing effects: First, it leads to a greater diffusion gradient allowing for more lactate to diffuse out of the muscle cell; second, it also increases the distribution space, which is reflected in the lower [La^-] (Figure 9 C). However, this does not consider simultaneous lactate extraction and net release within the same muscle fibre types of the same exercising muscle groups. In endurance-trained individuals, where this mechanism can be substantially enhanced, this would lead to a reduced systemic La^- that further reduces the measured [La^-] in addition to their larger BV.

Contribution of ECV and PV to lactate transport: [La^-] are normally measured in the whole blood. However, erythrocytes show a lower [La^-] when compared to plasma [La^-]. This difference in [La^-] between plasma and erythrocytes was found to be 1:0.5 under resting conditions but is augmented by strenuous exercise, i.e., 1:0.2 *(182)*. Accordingly, both volumes are contributing to the distribution of lactate at submaximal exercise intensities. With increasing exercise intensity, however, the aforementioned ratio changes substantially making the plasma volume almost exclusively responsible for the lactate transport at maximal exercise *(190)*. The significant reduction in plasma volume further decreases blood lactate transport capacity. We have calculated that even when a more cautious ratio of 1:0.3 is used, the lactate transport capacity in the BV at maximum exertion was still significantly reduced by 10.8 % exclusively as a result of the PV reduction (Figure 8). It was previously argued that the erythrocyte membrane provides a barrier to the flux of lactate between PV and ECV during rapidly changing blood lactate levels *(190)*. Thus, in addition to the well-known thermoregulatory and cardiovascular disadvantages of a reduced plasma volume *(191,192)*, our findings imply that it may also have a detrimental effect on lactate transport capacity.

Confounding factors: Two of our subjects with nearly identical La^-_{end} (1.02 vs. 1.04 $mmol \cdot kg^{-1}$) showed distinct differences in BVend when indexed for lean body mass (94.2 and 116.5 $mL \cdot kg^{-1}$), thus leading to different $[La^-]_{end}$ (10.9 and 8.9 $mmol \cdot L^{-1}$). However, these two participants also differed in their $\dot{V}O_{2max}$ (36.2 and 59.4 $mL \cdot min^{-1} \cdot kg^{-1}$) and P_{max} (3.2 and 5.0 $W \cdot kg^{-1}$), respectively. Since their La^-_{end} were identical, the differences in $[La^-]_{end}$ in these individuals can most likely be attributed to different blood volumes. Therefore, in order to understand the relationship between [La^-] and La^-, a more holistic approach is required. As mentioned before, the maximum systemic lactate concentration, e.g., when measured in the capillary blood, is always the result of lactate production, exchange, and utilisation *(167,193)* and the absolute amount of lactate in the blood depends on the interaction between the aforementioned factors.

With regard to the role of total BV, both intra- and inter-individual factors have to be considered. For instance, it was demonstrated particularly in endurance-trained individuals that the lower blood [La^-] is usually the combined result of a training-induced decrease in the overall release of lactate from tissues to blood as well as an increase in clearance from plasma during exercise *(194)* equalling a lower absolute La^- in the blood. This is most likely due to an increase in mitochondrial monocarboxylate transporters and enzymatic lactate dehydrogenase activity which in turn improves the oxidative capacity of the muscle cells *(195)*. In addition to their

large BV, these adaptations most likely lead to chronically lower [La^-] during dynamic exercise.

Similar conditions can also be observed on the inter-individual level, e.g., in trained athletes from different disciplines. While athletes participating in sports requiring explosive muscular power, e.g., sprinting exercise, usually possess a larger quantity of high glycolytic fibre types, elite endurance athletes are characterised by a much higher percentage of oxidative fibres. Additionally, sprinters are characterised by a lower BV when compared to endurance-trained athletes *(74)*. Moreover, their PV losses are typically larger than during endurance exercise reducing the most effective distribution medium for La^- even further *(196)*. This would suggest that the usually higher [La^-] found in sprinters at a higher power do not necessarily indicate a higher absolute blood La^- when compared to endurance-trained athletes. The same would eventually apply for inter-individual comparisons between untrained individuals with different BV, e.g., due to genetic predisposition *(78)*.

Practical Implications: Although BV is not routinely determined in most exercise labs, this study highlights its general relevance in the context of lactate diagnostics and the interpretation of results. In terms of blood lactate diagnostics in exercise testing and training it should be noted, that the PV can increase by up to 15 % as a result of systematic endurance training *(3)*; while the ECV can increase by up to 6 % *(197,198)*. Notably, the PV significantly increases after just very short time periods (hours to days), thus increasing the potential distribution volume rapidly long before metabolic adaptations take place *(2)*. Therefore, the increases in BV should also be considered in the interpretation of changes in lactate kinetics, especially when (long-term) training interventions are conducted. This is independent of the fact that the percentage differences in La^- as a result of the exercise-induced PV shifts that we found in this study likely yield no practical importance for interpreting lactate kinetics. Moreover, our results underline the importance of ensuring an adequate hydration state before and during training and competition. Here, PV is important for supporting the homeostasis of cardiovascular and thermoregulatory systems *(199)*. For instance, it has been shown that an isotonic reduction in PV in turn leads to a reduction in sweat rate *(200)*. These findings may be of even greater importance when exercising in the heat *(201)* or monitoring exercise intensity using non-invasive biomarkers such as forehead sweat lactate secretion rate *(202)*. Lastly, it would be of great interest as to whether a threshold determination based on absolute systemic La^- indexed for lean body mass rather than [La^-] could be a viable option in the context of lactate performance diagnostics.

Limitations: There are several limitations to this study. First, when interpreting our data, it is important to consider that our assumptions have been made on selected exercise intensities during an incremental CPX test, i.e., $P_{60\%}$ and P_{max}. Second, it may well be that the dependencies between the BV, La^- and $[La^-]$ diverge with regard to different exercise modalities, e.g., during a Wingate test, high-intensity interval exercise, or a continuous moderate exercise, due to different lactate fluxes from working muscles to the bloodstream, different ratios between PV and erythrocytes, or different fluxes of lactate to consuming tissues *(186)*. Third, our study population consisted exclusively of heterogeneously trained female participants. Although we would hypothesise that the same mechanisms also apply to men, especially since it was demonstrated that their BV shifts are typically much larger *(36,82,133)*, we have not controlled for the menstrual cycle which has been shown to have an influence on water retention, and thus plasma volume *(203)*. Moreover, inter-individual differences in training status may also have affected the rate of lactate production and clearance during exercise thus affecting our results *(204)*.

Conclusions: In this study, we evaluated the influence of blood volume and absolute systemic lactate quantity on the lactate concentrations during an incremental CPX test in healthy individuals. Our findings demonstrate that a higher BV was associated with a lower $[La^-]$ at maximum exercise. Since the $[La^-]$ between erythrocyte and plasma substantially differ during intensive exercise, acute plasma volume changes also have a substantial influence on the lactate transport capacity in the total blood volume. In addition to its influence on cardiovascular and thermoregulatory stability, our data indicate that another important property can be attributed to PV.

9 Artikel IV: Plasma Volume Shifts and Acid-Base Balance after a Single Bout of Resistance Exercise

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Abstract

Changes in plasma volume (PV), acid-base status and ventilation have rarely been investigated in relation to resistance training (RT). This study aimed to investigate the effect of a single set of exhaustive leg press exercise on these basic physiological parameters in an integrated manner.

27 healthy, male individuals (27.1 ± 4.1 years, 1.82 ± 0.62 m, 84.4 ± 12.5 kg) performed a single set of horizontal leg press exercise until volitional exhaustion during which hemoglobin concentration ([Hb]), hematocrit (Hct) as well as pH, hydrogen carbonate ($[HCO_3^-]$) and lactate concentrations ($[La^-]$) were determined until 15-minutes post-exercise. Total buffer capacity was calculated based on pH, $[HCO_3^-]$ and pCO_2. Hemoglobin mass for the calculation of blood volume (BV) was determined twice using a carbon monoxide re-breathing method.

Mean PV decreased by 559 ± 230 mL (13.7%) and was still significantly decreased at 15-minutes post-exercise. Changes in PV led to hemoconcentration which in turn significantly increased arterial oxygen content ($p<0.001$). At exhaustion, pH (7.30 ± 0.06), $[HCO_3^-]$ (18.6 ± 2.0 $mmol \cdot L^{-1}$) and SBE (−6.6 ± 2.4 $mmol \cdot L^{-1}$) were all significantly decreased compared to baseline ($p<0.0001$) while pCO_2 (39.4 ± 4.3 mm Hg) was unchanged. With the immediate and significant increase in $\dot{V}E$ after exhaustion, pCO_2 was significantly decreased one-minute post-exercise (34.4 ± 4.2 mm Hg), indicating metabolic acidosis with respiratory compensation, which was maintained until t_{+15}. During post-exercise recovery, non-bicarbonate buffering remained constant while the respiratory component steadily increased from t_{+3} (35.0 $mmol \cdot L^{-1}$ per pH) until t_{+15} (50.2 $mmol \cdot L^{-1}$ per pH).

Following a single set of horizontal leg press exercise in healthy, trained individuals, PV is reduced by ~560 mL corresponding to ~14% hereby improving post-exercise arterial oxygen content due to hemoconcentration. RT leads to moderate metabolic acidosis, which, however, was not compensated during exercise because of restricted breathing but partly compensated during the following 15-minute recovery period. The respiratory compensation as part of the bicarbonate buffering made up 50% of total buffer capacity in the course of recovery.

Keywords: pH, bicarbonate, lactate, acidosis, PV correction, blood volume, hemoglobin concentration, hematocrit

Introduction

Resistance training (RT) is commonly prescribed to increase underlying strength and power qualities in an attempt to improve athletic performance *(205)*. In recent years, research in the field of RT has dealt in depth with the associated hormonal *(206,207)*, morphological *(208,209)* and neuronal adaptations *(210,211)*, as well as the molecular determinants of skeletal muscle hypertrophy and force production *(212,213)*. However, first and foremost, any exercise stimulus leads to fundamental vegetative-physiological, e.g., cardiovascular, metabolic and respiratory changes that are linked to chronic adaptations and an increase in exercise performance. While many of these physiological mechanisms have been extensively studied in endurance training, much is still unknown with regard to RT.

These mechanisms include, for instance, exercise-induced changes in plasma volume (PV). It is well known that during short duration and high-intensity or prolonged aerobic exercise, PV undergoes intricate alterations, which are influenced by factors such as changes in intravascular pressure, osmotic regulation or sweat loss leading to exercise-induced changes between 5-22% *(38–40,47,214,215)*. In addition, especially during RT, muscle metabolism with regard to lactate production and elimination plays an important role. PV changes have only been previously reported as percentage changes which complicates the understanding of the magnitude and temporal dynamics of PV shifts. This is further illustrated by previous research demonstrating that PV shifts are associated with changes in cardiac output and oxygen delivery *(83,183,216)*, as well as nutrient transport to exercising muscles *(217)* and maybe even lactate transport capacity *(218)*. The latter is of particular importance as it also directly influences acid-base balance *(87,219)*.

In this context, it is well known that RT can lead to marked alterations in blood pH and lactate concentrations that have been associated with substantial changes in ventilation. At the same time, buffer capacity reflected in bicarbonate and non-bicarbonate buffering, is also substantially altered when exercising to volitional exhaustion. Taking the pCO_2 into account, the share of the respiratory component in the defence of the pH value can then be determined. To the best of our knowledge, this has not yet been done. To allow for a more holistic understanding of hematological, metabolic and respiratory regulations during RT, this study aimed to determine exercise-induced changes in PV as well as changes in acid-base balance, total buffer capacity and ventilation during and after a single bout of RT in healthy, trained male individuals.

Methods

Participants: 27 healthy, male individuals with a mean age of 27.1 ± 4.1 years, height of 1.82 ± 0.62 m, body mass of 84.4 ± 12.5 kg (BMI: 25.4 ± 3.0 $k \cdot gm^{-2}$), skeletal muscle mass of 41.1 ± 5.4 kg (48.9 ± 3.3 %) and fat mass of 13.1 ± 6.3 kg (15.1 ± 5.5 %) participated in this study. Eligibility criteria included male individuals with no history of cardiac disease who have been following a self-reported resistance exercise training program including a minimum of two sessions per week for a minimum of one year. Inclusion and exclusion criteria were assessed by the same researcher prior to the start of the study. All investigations were conducted in accordance with the Declaration of Helsinki on ethical principles for medical research on humans and guidelines for Good Clinical Practice and the test protocol was approved by the local ethics committee of the University of Bayreuth (Ethics-No: 23-017). Before any trial related activities, all participants provided written informed consent, which included the aims and risks of the study. Participants were allowed to withdraw from the study at any time without further explanations.

Horizontal leg press: Upon arrival at the research facility, lean body mass and fat mass were measured twice consecutively using a bioelectrical impedance analysis (InBody 720, InBody Co., Seoul, South Korea). Afterwards, participants were introduced to the horizontal leg press (Cybex Strength Systems, Rosemont, U.S.A.) and their individual starting position was determined, which was set so that the knee angle was slightly below 90 degrees ensuring standardized range of motion. Participants were informed that the movement speed was predetermined as 2 seconds for the eccentric and concentric phase, respectively, equaling 4 seconds for one full repetition. Movement velocity was acoustically demonstrated using a metronome. Participants then had to remain in a seated position for ten minutes before a warm-up protocol of 20 repetitions with a standardized weight of 40 kg was performed. To control for posture effects on changes in PV in the post-exercise phase, participants were asked to once again remain in a seated position for 10 minutes. In order to elicit larger metabolic alterations, a time under tension (TuT) >90 seconds was targeted but not obligatory and participants were asked to select a weight of their own choice based on their personal experience in resistance training for the following set. One minute before the start of the exercise, participants were asked to enter the leg press and wait for the countdown. Repetitions were initially performed according to the acoustic feedback signal with standardized repetition duration. However, termination of exercise was defined as the moment at which no further voluntary muscular contraction was possible independent of the repetition duration with participants receiving strong verbal encouragement to reach complete physical exhaustion. Upon completion of the last repetition, participants

initially remained within the horizontal leg press for 1 minute before they transferred in a seated position and remained there until 15 minutes post exercise to control posture effects on PV shifts.

Blood gas analysis, acid-base status and spirometry: Capillary blood samples were taken from a hyperemized earlobe at rest, immediately after exhaustion as well as 1-, 3-, 5-, 7-, 10- and 15-minutes post exercise to determine carbon dioxide partial pressure (pCO_2), oxygen partial pressure (pO_2), oxygen partial pressure at which hemoglobin is 50% saturated (p50), pH, hydrogen carbonate ($[HCO_3^-]$), standard bicarbonate (SBC), actual base excess (ABE), standard base excess (SBE), capillary oxygen saturation (ScO_2), hemoglobin concentration ([Hb]) and hematocrit (Hct) using a portable, fully automated blood gas analyzer (ABL80 FLEX CO-OX - RiliBäK, Radiometer, Copenhagen, Denmark). At the same time points, capillary blood samples were taken from the other earlobe for the measurement of lactate ($[La^-]$) and glucose concentrations ($[Glu^-]$) (Biosen S-Line, EKF-Diagnostic, Barleben, Germany). To control for posture effects on the PV response, additional capillary blood samples were taken after the warm-up and just before the start of the leg press exercise. Total buffer capacity (β_{tot}), total bicarbonate (β_{bi}) and non-bicarbonate buffering (β_{nbi}) were calculated subsequently according to the following formulas based on the changes in $[La^-]$, pH, and $[HCO_3^-]$:

$$\beta_{\mathrm{tot}} = \Delta[\mathrm{La^-}]_{\mathrm{Pla}} \times \Delta\mathrm{pH}^{-1} \quad (1)$$

$$\beta_{\mathrm{bi}} = \Delta[\mathrm{HCO_3^-}] \times \Delta\mathrm{pH}^{-1} \quad (2)$$

$$\beta_{\mathrm{nbi}} = (\Delta[\mathrm{La^-}]_{\mathrm{Pla}} \times \Delta\mathrm{pH}^{-1}) - (\Delta[\mathrm{HCO_3^-}] \times \Delta\mathrm{pH}^{-1}) \quad (3)$$

Using formula 2 and the equation $\Delta pCO_2 \times \Delta pH^{-1} = 1.04 + \beta_{nbi} \times [HCO_3^-]$, we also distinguished between the respiratory (β_{bi_r}) and non-respiratory (β_{bi_nr}) component of the bicarbonate buffer *(88)*. The $[La^-]$ in the plasma was calculated based on blood $[La^-]$ using a ratio between $[La^-]$ in the erythrocyte and in the plasma of 0.78:1 at rest, 0.45:1 at maximum exercise and 0.5:1 during recovery considering the prevailing Hct *(220)*. Blood acid-base status was defined according to the alignment nomogram by Siggaard Andersen *(89,90)*. Arterial oxygen content (CaO_2) was calculated according to the following formula where 1.39 = Huefner number:

$$\mathrm{CaO_2\ (mL \cdot dL^{-1})} = \mathrm{[Hb]\ (g \cdot dL^{-1})} \times \mathrm{SpO_2\ (\%)} \div 100 \times 1.39\ \mathrm{(mL \cdot g^{-1})} \quad (4)$$

A portable, high resolution spiroergometry system with breath-by-breath technology (Metamax® 3B, Cortex Biophysik GmbH, Leipzig, Germany) was used for the continuous measure-

ment of ventilation ($\dot{V}E$), oxygen uptake and ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$). Additionally, tidal volume ($\dot{V}T$), respiratory rate and respiratory exchange ratio (RER) were also quantified. Hereinafter, quantitative changes of the aforementioned variables are given in relation to their respective measurement time points, which are titled as follows: t_{rest} for resting values, t_{Exh} for immediately after exhaustion, as well as t_{+1}, t_{+3}, t_{+5}, t_{+7}, t_{+10} and t_{+15}, for 1-, 3-, 5-, 7-, 10-, and 15-minutes post exercise, respectively. Additionally, data for spirometric parameters are also presented in 5-second intervals between t_{Exh} and t_{+1}. All other parameters were averaged over a period of 30 seconds (15 seconds before and after the respective measurement time point), whereas peak values, e.g, $\dot{V}O_{2peak}$, are given as the highest 30-second interval.

Hemoglobin mass and total blood volume: The total hemoglobin mass (Hbmass) as well as blood (BV), plasma (PV) and erythrocyte volumes (RCV) were determined twice within 5 days from the leg press exercise using the optimized CO-rebreathing method according to the methods reported previously *(50,51,114)*. In brief, an individual dose of carbon-monoxide (CO, 0.8-1.0 mL·kg^{-1}, CO 3.7, Linde AG, Unterschleißheim, Germany) was administered and rebreathed along with 3 L of pure medical oxygen (Med. O_2 UN 1072, Rießner-Gase GmbH, Lichtenfels, Germany) for 2 minutes. Capillary blood samples were taken before and 6- and 8-minutes post administration of the CO dose and analyzed for the percentage of carboxyhemoglobin (%HbCO) using a blood gas analyzer (ABL80 FLEX CO-OX RiliBäK, Radiometer, Copenhagen, Denmark). The Hbmass was calculated based on the mean change in %HbCO before and after the rebreathing procedure. Subsequently, the total BV was calculated based on the Hbmass and the [Hb] and the PV was calculated based on the total BV and erythrocyte volume (ECV) according to the following formulas:

$$\mathrm{BV\ (mL)} = \mathrm{Hbmass\ (g)} \times 100 \div [\mathrm{Hb}]\ (\mathrm{g \cdot dL^{-1}}) \div 0.91 \quad (5)$$

$$\mathrm{EZV\ (mL)} = \mathrm{Hbmass\ (g)} \div ([\mathrm{Hb}]\ (\mathrm{g \cdot dL^{-1}}) \div \mathrm{Hct} \times 100) \times 100 \quad (6)$$

$$\mathrm{PV\ (mL)} = \mathrm{BV\ (mL)} - \mathrm{ECV\ (mL)} \quad (7)$$

where [Hb] = venous hemoglobin concentration and 0.91 = cell factor at sea level representing the ratio between central and peripheral hematocrit *(52)*. Hematological variables, e.g., [Hb], Hct and PV are also referred to in relation to their measurement times as described above. Since the Hbmass does not change over short periods of time, the temporally offset determination of the [Hb] for the calculation of the BV is possible without compromising accuracy *(56)*. The typical errors for Hbmass and BV in our laboratory are 1.5% and 2.5%, respectively, which is comparable to previous investigations *(116,117)*.

Statistical analysis: The data are presented as means and standard deviations. Statistical analysis was conducted using GraphPad Prism Version 8.0.2 (GraphPad Software, Inc., San Diego, U.S.A.). Testing for normality was performed using the Shapiro-Wilk test. On the basis of these results, a repeated measures ANOVA or mixed-effects analysis followed by Tukey's multiple comparisons tests was performed to prove any significant differences between time points. A repeated measures two-way ANOVA or mixed-effects analysis followed by Tukey's multiple comparisons tests was performed to prove any significant differences between measured values and values corrected for PV changes. Pearson's product moment correlations were performed to prove any relationship between two variables. The level of significance was set to $p \leq 0.05$ and p-values are presented as * ($p \leq 0.05$), ** ($p \leq 0.01$) and *** ($p \leq 0.001$).

Results

Leg press exercise: The mean selected weight in the horizontal leg press was 127 ± 22.8 kg equalling 151 ± 23 % of body mass. TuT ranged between 75 and 250 s (129 ± 43 s) and maximum heart rate was 157 ± 11.2 bpm. At t_{Exh}, TuT was significantly correlated with RER (1.26 ± 0.13, r=0.58, p=0.001), [La^-] (7.20.32 ± 1.73 mmol·L^{-1}, r=0.58, p=0.001), pH (7.30 ± 0.06, r=−0.3, p=0.17) and HCO_3^- (18.6 ± 2.0. mmol·L^{-1}, r=−0.41, p=0.04) but not pCO_2 (39.4 ± 4.3 mm Hg, r=0.03, p=0.88).

PV, [Hb], Hct: Total BV and Hbmass were 6938 ± 773 mL (83 ± 8.5 mL·kg^{-1}) and 949 ± 129 g (11.3 ± 1.2 g·kg^{-1}), respectively. Compared to t_{rest}, PV was significantly decreased until t_{+15} (4046 ± 405 vs. 3753 ± 380 mL, p<0.01) with a maximum decrease observed at t_{+3} (−559 ± 229 mL, −13.7 %, see Fig. 10). Individual, maximum percentage changes in PV (ΔPV) ranged between −2.9 and −23.9 % (−123 and −1091 mL) and were not correlated with the lowest pH values (r=0.25, p=0.22), $[La^-]_{max}$ (r=−0.23, p=0.24) or TuT (r=0.02, p=0.89). We also found no correlation between ΔPV and resting PV (r=0.07, p=0.36) or BV (r=0.05, p=0.40). As a result of the PV decrease, both capillary [Hb] (15.6 ± 0.7 vs. 16.9 ± 1.1 g·dL^{-1}, p<0.0001) and Hct (48.0 ± 2.0 vs. 51.8 ± 3.3 %, p<0.0001) significantly increased between t_{rest} and t_{Exh} and remained significantly increased until t_{+15} (p<0.05). For both [Hb] (17.2 ± 1.0 g·dL^{-1}) and Hct (52.4 ± 3.2%), maximum values were obtained at t_{+3}.

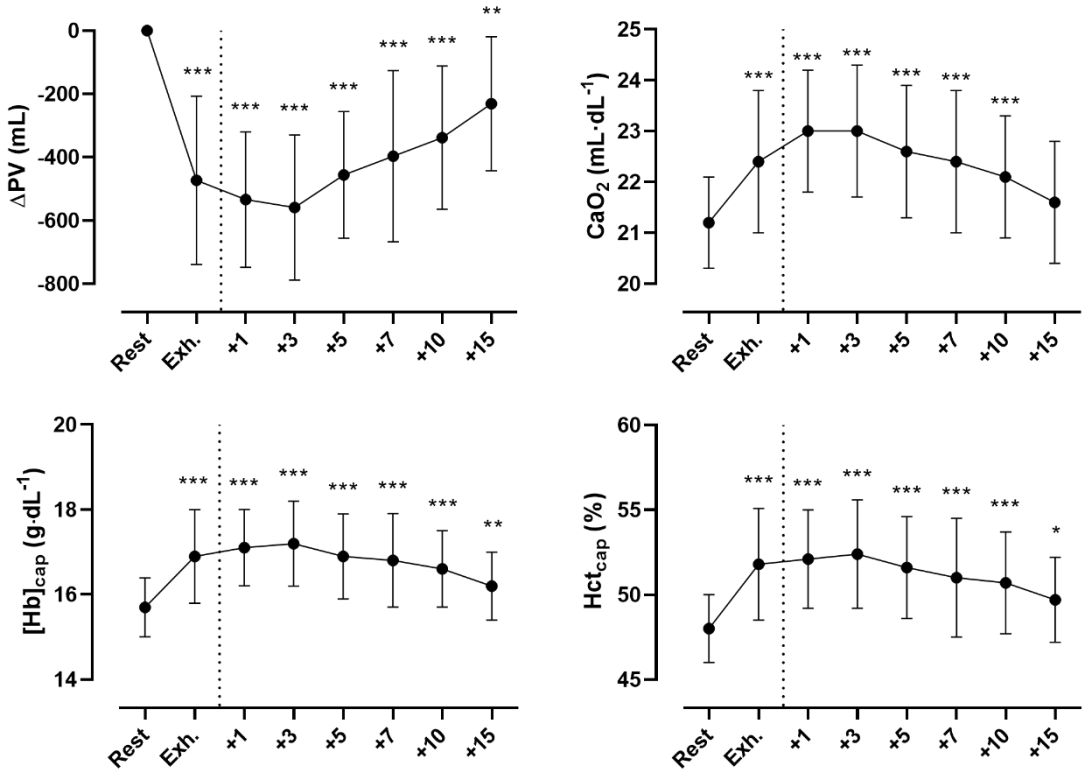

Abbildung 10. Exercise-induced changes in plasma volume (ΔPV), arterial oxygen content (CaO_2), hemoglobin concentration ([Hb]) and hematocrit (Hct) during and after single set leg press exercise ($^{*}p\leq0.05$, $^{**}p\leq0.01$ and $^{***}p\leq0.001$ indicate significant compared to resting value).

Acid-base balance: pH significantly decreased between t_{rest} and t_{Exh} (7.42 ± 0.02 vs. 7.30 ± 0.06, p<0.0001) and remained decreased until t_{+15} (7.31 ± 0.06, p<0.0001, see Fig. 11). Lowest mean values were observed at t_5 (7.24 ± 0.05). [La^-] were significantly increased until t_{+15} (1.0 ± 0.3 mmol·L^{-1} vs. 8.9 ± 2.2 mmol·L^{-1}, p<0.0001, Fig. 11) when compared to t_{rest} with peak values observed at t_{+5} (11.3 ± 1.8 mmol·L^{-1}). pH and [La^-] were significantly negatively correlated at all post-exercise measurement points (e.g., r=−0.72, p<0.0001 at t_{+5}). HCO_3^- (24.6 ± 1.3 vs. 18.6 ± 2.0 mmol·L^{-1}, p<0.0001) and ABE significantly decreased between t_{rest} and t_{Exh} and remained decreased until t_{+15} (all p<0.0001). Lowest values were found at t_{+5}, respectively (see Tab. 12).

The pO_2 significantly increased between t_{rest} and t_{+10} (91.0 ± 5.5 vs. 97.0 ± 7.9 mm Hg) and the highest value was found at t_{+1} (108 ± 9.1 mm Hg, see Tab. 12). The pCO_2 showed no change between t_{rest} and t_{Exh} but a significant decrease between t_{Exh} and t_{+1} (39.4 ± 4.3 vs. 34.4 ± 4.2

mm Hg, p<0.0001) and t_{+3} (31.3 ± 3.5 mm Hg, p<0.0001), respectively. Lowest pCO_2 values were obtained at t_{+7} (30.6 ± 3.1 mm Hg). At t_{+15}, pCO_2 was still significantly decreased compared to t_{rest} (32.4 ± 2.7 mm Hg, p<0.0001). ScO_2 slightly but significantly decreased between t_{rest} and t_{Exh} (97.3 ± 0.7 % vs. 96.1 ± 0.9 %, p<0.0001) and remained decreased until t_{+15} (95.7 ± 1.2, p<0.01, see Tab. 12). CaO_2 was significantly increased between t_{rest} and t_{Exh} (21.2 ± 0.9 vs. 22.4 ± 1.4 $mL \cdot dL^{-1}$, p<0.001). Highest values were obtained at t_{+3} and t_{+5} and CaO_2 remained significantly increased until t_{+10}. (p<0.0001, see Fig. 10). The p50 was significantly increased between t_{rest} and t_{Exh}. Highest values were obtained at t_{+5} (see Tab. 12) and p50 remained increased until t_{+15} (p<0.0001, see Fig. 11).

Total buffer capacity (β_{tot}), which is composed of bicarbonate (β_{bi}) and non-bicarbonate buffering (β_{nbi}), is shown in Tab. 11. The β_{nbi} was largest at t_{Exh} (25.2 ± 7.9 $mmol \cdot L^{-1}$ per pH unit) while no respiratory compensation was detected (β_{bi_r} = 1.1 ± 0.13 $mmol \cdot L^{-1}$ per pH unit). During post-exercise recovery, β_{nbi} remained on a constant lower level while the respiratory component (β_{bi_r}) steadily increased from t_{+1} (23.8 ± 13.1 $mmol \cdot L^{-1}$ per pH unit) until t_{+15} (50.2 ± 18.3 $mmol \cdot L^{-1}$ per pH unit).

Tabelle 11. Calculated post-exercise total buffer capacity (β_{tot}), non-bicarbonate (β_{nbi}) and bicarbonate buffering including respiratory (β_{bi_r}) and non-respiratory (β_{bi_nr}) component (numbers in brackets represent the percentage of β_{tot}).

Timepoint	Total buffer capacity (β_{tot})	Non-bicarbonate buffering (β_{nbi})	Bicarbonate buffering (β_{bi_nr})	Bicarbonate buffering (β_{bi_r})
t_{Exh}	75.8 ± 29.1	25.2 ± 7.9 (33.3%)	49.5 ± 14.8 (65.3%)	1.1 ± 0.13 (1.4%)
t_{+1}	77.5 ± 15.3	18.0 ± 6.7 (23.3%)	35.6 ± 7.8 (46.0%)	23.8 ± 13.1 (30.7%)
t_{+3}	80.8 ± 15.3	15.3 ± 4.1 (18.9%)	30.5 ± 6.5 (37.8%)	35.0 ± 18.5 (43.3%)
t_{+5}	79.2 ± 11.1	14.7 ± 2.8 (18.6%)	30.5 ± 5.0 (38.5%)	34.0 ± 14.5 (42.9%)
t_{+7}	81.2 ±13.3	14.1 ± 5.6 (17.3%)	29.6 ± 4.6 (36.5%)	37.5 ± 16.2(46.2%)
t_{+10}	87.9 ± 13.5	15.1 ± 3.8 (17.2 %)	28.9 ± 5.3 (32.9%)	43.9 ± 18.5 (49.9%)
t_{+15}	98.2 ± 21.6	18.7 ± 5.3 (19.0%)	29.3 ± 6.2 (29.8%)	50.2 ± 18.3 (51.2%)

Data are presented as mean ± standard deviation. Buffer capacity is measured as $mmol \cdot L^{-1}$ per pH unit *(221)*.

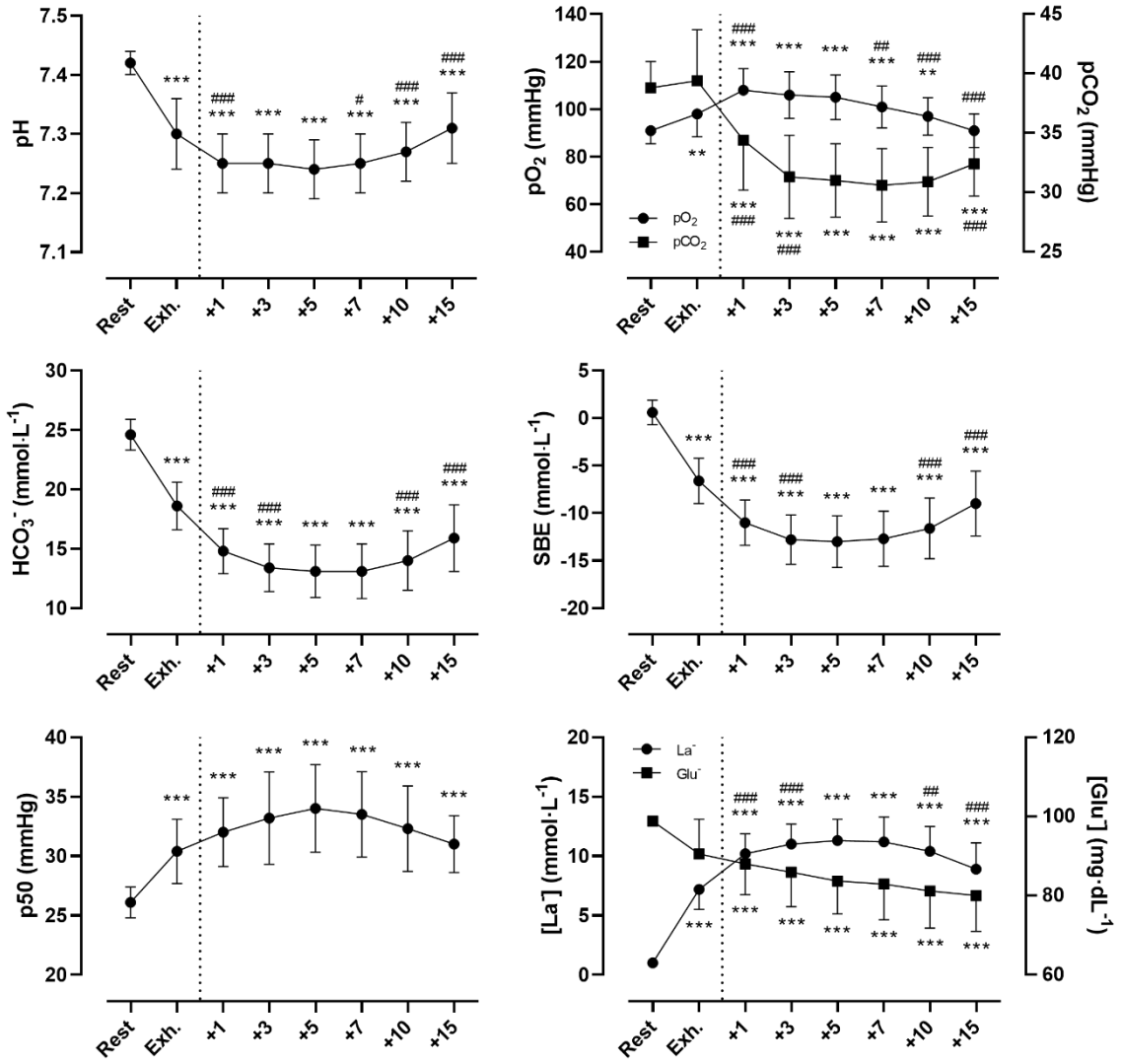

Abbildung 11. Measured blood gases and acid-base parameters during and after single set leg press exercise ($^{*}p\leq0.05$, $^{**}p\leq0.01$ and $^{***}p\leq0.001$ indicate significant compared to resting value; $^{\#}p\leq0.05$, $^{\#\#}p\leq0.01$ and $^{\#\#\#}p\leq0.001$ indicate significant compared to previous value).

Tabelle 12. Resting and peak mean values of acid-base, blood gas, spirometric and hematological parameters.

	Rest			***Peak***		
	Mean±SD	**Min**	**Max**	**Mean±SD (t_x)**	**Min**	**Max**
$[La^-]$ ($mmol \cdot L^{-1}$)	0.99 ± 0.25	0.64	1.57	11.32 ± 1.79 (t_{+5})	7.28	14.72
$[Glu^-]$ ($mg \cdot dL^{-1}$)	98.8 ± 12.8	80.2	120.4	80.1 ± 9.1 (t_{+15})	56.0	94.2
pH	7.42 ± 0.02	7.38	7.49	7.24 ± 0.05 (t_{+5})	7.14	7.32
HCO_3^- ($mmol \cdot L^{-1}$)	24.6 ± 1.3	21.6	27.5	13.1 ± 2.2 (t_{+5})	8.7	19.0
SBC ($mmol \cdot L^{-1}$)	25.1 ± 1.1	22.7	27.2	14.8 ± 2.0 (t_{+5})	11.1	19.2
ABE ($mmol \cdot L^{-1}$)	0.7 ± 1.3	−2.0	3.2	−13.1 ± 3.1 (t_{+5})	−19.6	−6.5
pO_2 (mm Hg)	91.0 ± 5.5	78	105	108 ± 9.1 (t_{+1})	90	126
pCO_2 (mm Hg)	38.8 ± 2.2	32.5	42.8	30.6 ± 3.1 (t_{+7})	22.6	38.8
p50 (mm Hg)	26.1 ± 1.3	24	29	34.0 ± 3.7 (t_{+5})	28	41
$\dot{V}O_2$ ($L \cdot min^{-1}$)	0.62 ± 0.11	0.38	0.82	2.32 ± 0.44 (t_{Exh})	1.62	3.18
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	0.54 ± 0.10	0.37	0.85	2.92 ± 0.61 (t_{Exh})	1.83	3.97
RER	0.85 ± 0.07	0.73	0.96	1.68 ± 0.12 (t_{+1})	1.44	1.88
$[Hb]_{cap}$ ($g \cdot dL^{-1}$)	15.7 ± 0.7	14.5	16.9	17.2 ± 1.0 (t_{+3})	15.1	19.5
$[Hct]_{cap}$ (%)	48.0 ± 2.0	44.5	51.8	52.4 ± 3.2 (t_{+3})	46.2	59.5
ScO_2 (%)	97.3 ± 0.7	95.5	98.8	96.0 ± 1.0 (t_{+10})	93.9	98.7
CaO_2 ($mL \cdot dL^{-1}$)	21.2 ± 0.9	19.8	23.0	23.0 ± 1.2 (t_{+1})	20.8	25.5
PV (mL)	4046 ± 405	2831	4631	3463 ± 397 (t_{+3})	2366	4167
BV (mL)	6938 ± 773	4733	8294	6355 ± 779 (t_{+3})	4391	7510

SD=standard deviation, Min=minimum, Max=maximum, t_x=time point of the peak value, $[La^-]$=lactate concentration, $[Glu^-]$=glucose concentration, HCO_3^-=hydrogen carbonate, SBC=standard bicarbonate, ABE=actual base excess, pO_2=oxygen partial pressure, pCO_2=carbon dioxide partial pressure, $\dot{V}O_2$=oxygen uptake, $\dot{V}CO_2$=carbon dioxide output, RER=respiratory exchange ratio, $[Hb]_{cap}$=capillary hemoglobin concentration, $[Hct]_{cap}$=capillary hematocrit, ScO_2=capillary oxygen saturation, CaO_2=arterial oxygen content, PV=plasma volume, BV=blood volume.

Spirometry: $\dot{V}E$ significantly increased from t_{rest} to t_{Exh} (18.9 ± 3.7 vs. 84.6 ± 18.5 $L \cdot min^{-1}$, $p<0.0001$). Compared to t_{Exh}, $\dot{V}E$ showed a further significant increase after the first 5 seconds after t_{Exh} ($p<0.001$, Fig. 12). $\dot{V}E$ remained significantly increased until t_{10} (25.2 ± 6.7, $p<0.01$, see Fig. 12). $\dot{V}O_2$ was significantly increased between t_{rest} and t_{Exh} (0.62 ± 0.11 vs. 2.32 ± 0.44 $L \cdot min^{-1}$, $p<0.0001$) and remained significantly increased until t_{+3} (0.96 ± 0.31 $L \cdot min^{-1}$, $p<0.0001$). $\dot{V}CO_2$ was significantly increased until t_{+5} when compared to t_{rest} (0.54 ± 0.10 vs. 0.84 ± 0.18 $L \cdot min^{-1}$, $p<0.0001$, see Fig. 12). Peak values for $\dot{V}O_2$ and $\dot{V}CO_2$ were 2848 $mL \cdot min^{-1}$ (34.1 ± 7.0 $mL \cdot min^{-1} \cdot kg^{-1}$) and 3640 $mL \cdot min^{-1}$ (43.6 ± 8.0 $mL \cdot min^{-1} \cdot kg^{-1}$), respectively (see Tab. 12). Compared to t_{rest}, RER was significantly increased at t_{Exh} (0.85 ± 0.07 vs. 1.26 ± 0.13, $p<0.0001$) and remained significantly increased until t_{+10} (0.99 ± 0.12, $p<0.05$) with maximum mean values observed at t_{+1} (1.65 ± 0.25, $p<0.0001$). Both respiratory rate and $\dot{V}T$ significantly increased between t_{rest} and t_{Exh} (21.3 ± 4.3 vs. 39.1 ± 8.9 and 0.83 ± 0.15 vs. 2.28 ± 0.65 mL, both $p<0.0001$). Thereafter, respiratory rate and $\dot{V}T$ demonstrated an opposing trend between t_{Exh} and t_{+1} (see. Fig. 12) with respiratory rate showing a significant decrease while $\dot{V}T$ was significantly increased. Respiratory rate remained significantly increased until t_{+3} ($p=0.03$) while $\dot{V}T$ was significantly increased until t_{+7} ($p<0.01$).

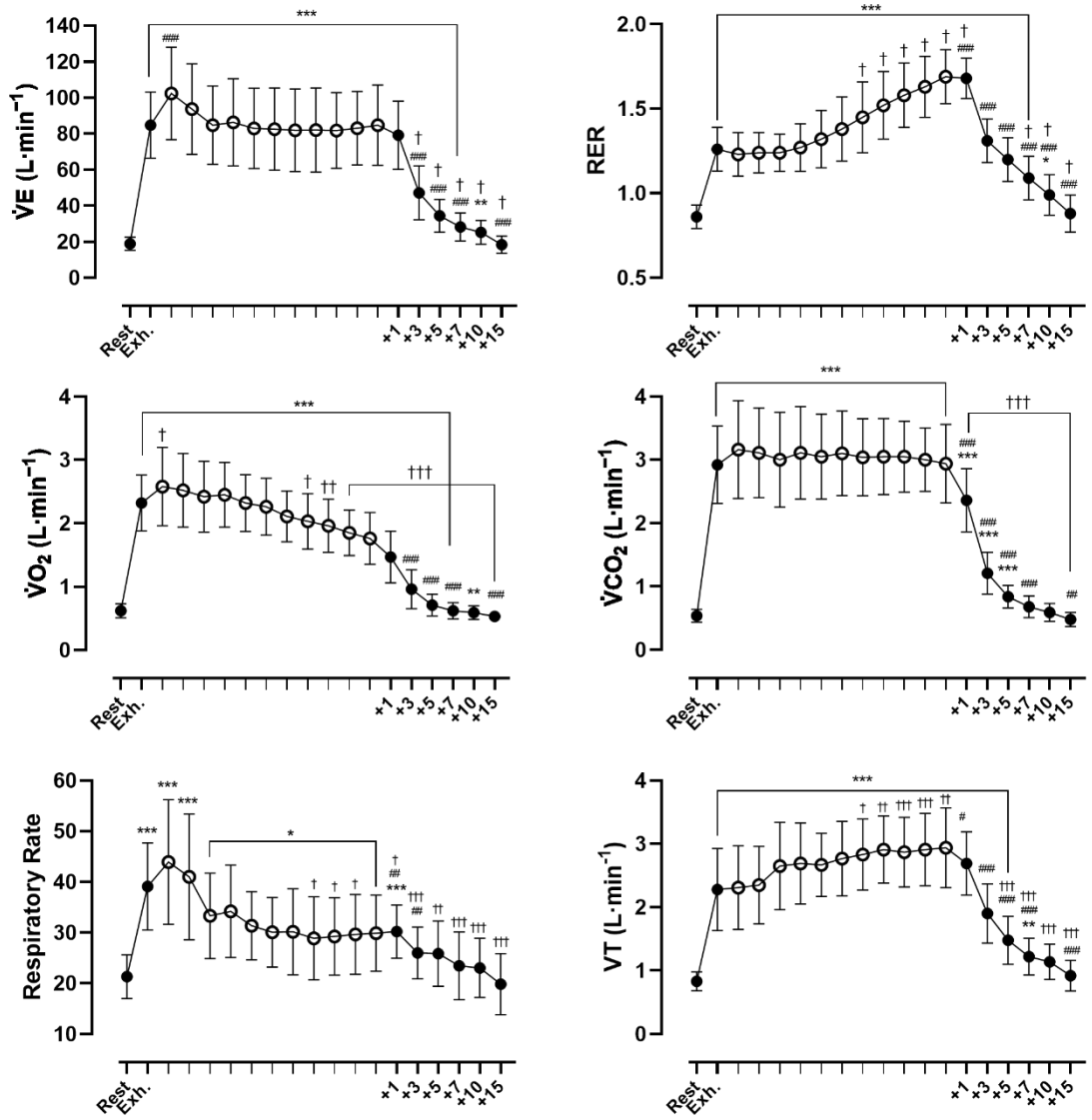

Abbildung 12. Ventilation ($\dot{V}E$), respiratory exchange ratio (RER), oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), respiratory rate and tidal volume ($\dot{V}T$) during and after single set leg press exercise (open circles indicate 5-second intervals between t_{Exh} and t_{+1}, $^{*}p\leq0.05$, $^{**}p\leq0.01$ and $^{***}p\leq0.001$ indicate significant compared to resting value; $^{\dagger}p\leq0.05$, $^{\dagger\dagger}p\leq0.01$ and $^{\dagger\dagger\dagger}p\leq0.001$ indicate significant compared to t_{Exh}; $^{\#}p\leq0.05$, $^{\#\#}p\leq0.01$ and $^{\#\#\#}p\leq0.001$ indicate significant compared to previous value).

Discussion and Conclusion

The aims of this study were to quantify the effect of RT on exercise-induced PV changes and the associated effects on oxygen transport, and to examine the acute changes in acid-base balance with special consideration of respiratory adaptation and buffer capacity. Our results demonstrate that mean PV was significantly reduced by −559 mL (~14%) and remained decreased until 15-minutes post-exercise. Due to the hemoconcentration, CaO_2 was significantly increased throughout the post-exercise period. Immediately at exhaustion, acid-base balance showed mild acidosis without respiratory compensation while from t_{+1} until t_{+15}, moderate acidosis with incomplete respiratory compensation was detected. The respiratory compensation as part of the buffering was increased by up to 50% in the course of recovery.

Plasma volume changes: There are several factors influencing the PV response during and after exercise, e.g., posture *(33,222)*, heat stress *(223,224)*, hydration *(225)* or the type of exercise itself *(183,215)*. Most studies have investigated the PV response during or after endurance-type exercise and only a handful of studies are available for RT. Moreover, these studies have only reported percentage changes in PV based on [Hb] and Hct. There, PV demonstrated a mean decrease between 0 and 22 % during and after RT, while most of the differences can be attributed to different protocols *(226)*. For instance, PV remained unaltered during constant load RT performed at lactate threshold intensity *(87)*, while Collins et al. demonstrated that PV was shown to decrease linearly in relation to exercise intensity, i.e., the percentage of the one-repetition maximum, i.e. 1-RM *(227)*. In contrast, Craig et al. found that a 10-RM protocol yielded a greater overall change in PV compared to a 5-RM protocol *(38)*, indicating that volume rather than intensity may influence the extent of PV changes during RT.

In this study our participants explicitly performed a single set of horizontal leg press exercise in order to eradicate the influence of inter-set rest or changes in posture on PV changes. Moreover, to the best of our knowledge, this is the first study to report absolute changes in PV during RT. In our study, mean maximum changes in PV were −559 ± 229 mL (−13.7 %), which is similar to what we previously observed in men after an exhaustive cardio-pulmonary exercise test (CPX) *(133)*. However, these values were observed at maximum exercise and do not reflect the total extent of PV shifts in the post-exercise phase. Based on the results in this study, it is reasonable to assume that PV shifts during and after a CPX are higher compared to a single set of RT. The PV shifts are generally the result of a greater filtration rate caused by an increase in blood pressure, sweat loss and especially lactate accumulation and the breakdown of creatine phosphate within the muscle cell *(38)*. The latter of which causes an increased osmotic gradient

that, in turn, leads to an influx of water into the intracellular and interstitial space *(41,228)*. At this point it must be stated that sweat and respiratory water losses are likely to be negligible in this study, as previous studies including several sets of RT showed no to minor changes in total body mass measured pre- and post-exercise *(40,229)*. Although posture may have an effect on PV changes during RT *(38)*, we found no changes in PV at rest, after warm-up or before the start of the single set exercise. Considering that our participants transferred from a seated into a supine position for the warm-up, we would argue that PV changes after t_{Exh} are not markedly influenced by posture effects.

Nonetheless, we observed a wide range of inter-individual changes in PV between −123 and −1091 mL (−2.9 and −23.9 %). This might in part be due to the large range of TuT, which, when repetition duration is controlled, serves as a correlate for repetition number and can be used as a marker for estimating exercise intensity, i.e., the percentage of an individual's 1-RM *(230)*. In this study, TuT ranged between 75 and 250 seconds indicating a vast range of an individual's 1-RM. However, we found no correlation between the maximum percentage changes in PV and TuT ($r=0.06$, $p=0.78$), lowest pH ($r=0.22$, $p=0.27$) or highest $[La^-]$ ($r=-0.25$, $p=0.21$). It is also possible that the systemic values of [Hb] that we measured could also be influenced by volume changes between non-exercising tissues as a result of the change in osmotic gradient attributing to the larges differences in PV shifts *(186)*.

As the data in Tab. 12 and Fig. 10 suggest, the participants in this study exercised to volitional muscular fatigue ensuring that they received a similar metabolic stimulus which in turn allows for inter-individual comparisons *(231)*. We would therefore conclude that the observed PV changes after a single set of leg press exercise are mainly the result of exercising to volitional muscular fatigue rather than exercise intensity.

PV changes and oxygen transport: The PV shifts induced a significant increase in [Hb] by 1.2 $g \cdot dL^{-1}$ at t_{Exh}, which was highest at t_{+3} (+1.5 $g \cdot dL^{-1}$, $p<0.0001$). At the same time, ScO_2 was significantly decreased by 1.2% ($p<0.0001$). In turn, both factors led to a significant increase in CaO_2 by 1.2 $mL \cdot dL^{-1}$ at t_{Exh} ($p<0.001$). This number is higher than what was previously reported during incremental cycling exercise in men *(216)*, which is explained by the smaller decrease in ScO_2 for similar [Hb] in this study. These findings confirm our previous assumption that the exercise-induced hemoconcentration more than compensates for the drop in ScO_2 serving as a physiological adjustment to improve arterial oxygen content and possibly performance *(183)*.

While $\dot{V}O_2$ demonstrated a significant increase from baseline compared to t_{Exh}, evidencing partially aerobic metabolism, it seems that $\dot{V}O_2$ during RT is impeded by frequent vasoconstriction *(93)*. The elevated $\dot{V}O_2$ between t_{Exh} and t_{+1} can be explained by replenishment of O_2 stores, i.e., myoglobin, and by increased aerobic metabolism, particularly by increased glycogen replenishment *(94)*. In the blood, these processes are facilitated by an increase in available O_2, as mentioned earlier. Moreover, as a result of metabolic acidosis, the O_2 dissociation curve (ODC), reflected in p50, is shifted to the right, which is known as the Bohr effect *(95)*. However, this right shift seems to have only a small negative effect on arterial O_2 saturation due to the increased pO_2 at t_{+1} and in the further course of exercise as a result of increased ventilation. On the other hand, the rightward shift of the ODC also improves O_2 delivery within the muscle cells. This process is further optimized by the fact that due to the restricted blood flow during RT, the pCO_2 within the muscle compartment increases massively as a result of the released lactate in the temporarily closed system *(95)*, thereby further decreasing pH and almost desaturating capillary blood. In this way, the exercise-induced reduction in PV and the concomitant metabolic acidosis allow for a more effective muscle oxygenation during and after RT, which, in theory, should also contribute significantly to muscular recovery between multiple sets of RT.

Acid-base balance and ventilation: The effect of moderate intensity RT on acid-base balance has been reported previously. For, instance, De Sousa et al. have demonstrated that pH remained unchanged during constant load resistance exercise at the lactate threshold *(87)*. Other studies demonstrated a progressive decline in pH during multiple sets of RT, i.e., leg press exercise *(86)* or following intermittent hand grip exercise *(232)*. In this study, we found a significant decrease in pH and a significant increase in $[La^-]$ until 15-minutes post-exercise (Fig. 11). Despite exercising to exhaustion, the changes in pH were substantially less than what was previously reported during maximal effort competitive rowing *(233)*. Compared to incremental treadmill running in men *(234)*, highest mean $[La^-]$ were lower in his study, which is most likely due to a larger metabolically active muscle mass during running exercise.

According to the alignment nomogram by Siggaard Andersen *(89,90)*, blood acid-base status at t_{Exh} can be described as moderate metabolic acidosis (pH = 7.30) without respiratory compensation (pCO_2 = 39.4 mmHg). At t_{+1}, however, blood status can be described as metabolic acidosis (pH = 7.26) with incomplete respiratory compensation (pCO_2 = 34.4 mm Hg) and this blood status is present until t_{+15}.

In theory, acidosis can be buffered in different ways. First, via non-bicarbonate buffers, which mainly happens through Hb and is of special importance in this study since PV changes induced an increase in [Hb]. Second, pH is also regulated via respiratory mechanisms, which have not yet been fully elucidated for both endurance and RT. However, lack of data is especially evident for RT. Considering the latter, pCO_2 was first unchanged with termination of exercise but then demonstrated a significant decrease until t_{+15}. The fact that the pCO_2 was unchanged at t_{Exh} can be explained by the partially impaired ventilation during RT as the rhythm of breathing is determined by the repetitions. This would also explain why $\dot{V}E$ was highest upon termination of exercise, mainly due to an increase in $\dot{V}T$, while respiratory rate quickly decreased (see Fig. 12). The observed maximum values of $\dot{V}E$ were similar to what was reported during a 30-sec Wingate tests *(92)*, however, they are still substantially lower than what was reported during incremental cycle exercise *(216)*. The hyperventilation during and after strenuous exercise is, at least in part, due to the simultaneous metabolic acidosis which results in the stimulation of peripheral chemoreceptors and so provides the extra drive to breathe *(235)*, therefore strongly contributing to the regulation of acid-base balance. This mechanism is also seen in patients with McArdle's disease, albeit their hyperventilation is associated with an increase in pH because of no underlying metabolic acidosis *(236)*.

For the first time, our data show the share of non-bicarbonate and bicarbonate buffering in total buffer capacity during a single bout of RT. Generally, our results are comparable to those presented by Böning et al., who calculated the total buffer capacity during incremental cycle exercise. This also applies to the temporal course of the different buffer components in the post-exercise phase *(88)*. However, in contrast to cycling exercise in the Böning study, we detected no respiratory compensation at t_{Exh}, which can possibly be explained by the aforementioned restriction of breathing during RT. In the further course of recovery, however, the respiratory component substantially increases (Tab. 2) and corresponds to the regulatory mechanisms known after endurance exercise. This culminates in a share of up to 50% of β_{tot} at the end of the recovery period. Since the non-bicarbonate buffer is also mainly based on Hb, the increase in [Hb] due to the PV shifts contributes to the metabolic buffering capacity by approx. 10%.

Our data illustrate an insufficient respiratory compensation during a horizonal leg press exercise, but a major effect of respiration on acid-base balance during recovery. From a practical point of view, these findings may be particularly relevant for multi-set resistance training. It is assumed that metabolic acidosis accumulates during the course of multi-set training, which is linked to progressive fatigue and a performance decrease in the following sets *(87,96)*. In RT, the inter-set rest usually between two and five minutes, depending on intensity and volume *(97)*.

However, in this study, metabolic acidosis was not only present after the set, but also 15 minutes thereafter, which would favour such an accumulation effect. Future studies should therefore investigate the effect of exercising smaller muscle groups, where breathing is not restricted, on the metabolic state in the post-exercise phase.

In summary, following a single set of horizontal leg press exercise in healthy, trained individuals, PV is reduced by ~560 mL (~14%) hereby improving post-exercise arterial oxygen content due to hemoconcentration. RT leads to moderate metabolic acidosis, which, however, was not compensated during exercise because of restricted breathing but partly compensated during the following 15-minute recovery period. The respiratory compensation as part of the buffering was increased by up to 50% of total buffering capacity in the course of recovery.

Limitations: We did not perform isometric or isotonic maximum strength testing to determine a standardized exercise stimulus, i.e., in terms of percentages of 1-RM. The weight was chosen by the participants themselves and solely based on their RT experience. Although it was previously demonstrated that a given number of repetitions is not always associated with the same percentages of the 1-RM *(237)*, our protocol led to a vast range of TuT. However, the metabolic and respiratory findings we observed in this study as well as PV changes were all independent of TuT. In contrast, the significant correlations that we found between TuT and RER or $[La^-]$ at t_{Exh}, respectively, are most likely explained by a higher repetition number with higher TuT. This was also demonstrated previously, where performing a training protocol with higher repetition numbers led to increased $[La^-]$ compared to a protocol with lower repetition numbers *(238)*. From a practical perspective, it seems that exercising until muscular exhaustion rather than TuT itself is more important in order to induce changes in acid-base balance.

Perspective

Physical exercise leads to a variety of acute adaptive responses that are not yet fully understood. For resistance training in particular, there have been very few studies to date that have looked at the integrative response of plasma volume shifts, acid-base status and ventilation. This study was the first to demonstrate that hemoconcentration caused by PV shifts is associated with an increase in arterial oxygen content as well as an increase in metabolic buffering capacity. In contrast to incremental endurance exercise, no respiratory compensation was observed during resistance training at the termination of exercise. In the post-exercise phase, however, the share of the respiratory component rises rapidly contributing up to 50 % of the total buffer capacity. Our results contribute to a more holistic understanding of the physiological regulation during resistance training.

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Verzeichnis eigener Publikationen und Konferenzbeiträge

I. Publikationen mit Peer-Review Verfahren als Erstautor

Schierbauer J, Zimmer R, Wachsmuth NB, Maassen N and Schmidt WFJ (2023). Plasma Volume Shifts and Acid-Base Balance after a Single Bout of Resistance Exercise. Submitted to: *Scandinavian Journal of Medicine & Science in Sports* (under review).

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