Intensive Care Med (2000) 26: S137–S144

H. Montgomery

Cardiac reserve: linking physiology and genetics

H. Montgomery
Dept. of Cardiovascular Genetics, Rayne Institute,
5, University Street, London WC 1E 6JJ

Introduction

Critical illness is generally associated with an increase in metabolic rate, and hence increased demand for both oxygen and metabolic substrates. The attempt to meet higher substrate demands requires an increase in delivery. Delivery to the cell may increase through elevated extraction as well as increased delivery to the microcirculation itself [1]. Amongst surgical patients, an increase in oxygen demand is initially met by increased extraction, and then by increased delivery using 'cardiac reserve' [2]. Cardiac reserve is defined as the difference between basal and maximal cardiac work. Both the magnitude of this reserve and its responsiveness to recruitment may have profound impact on the outcome of critical illness: failure to meet the increased metabolic demands of the tissues will result in (potentially deleterious) metabolic deficit.

This article will focus on the factors which regulate and limit cardiac reserve. A novel approach to improve the balance between substrate demand and delivery will be presented.

Normal cardiac physiology

During normal myocardial contraction, electrical depolarisation initiates, through the interactions of calcium, troponin and tropomyosin, the cross-bridging of actin with the two heads of the myosin molecule. This results in sarcomere shortening. The myosin heads also contain ATPase that is activated by contact with actin, releasing the energy for contraction. This myosin-bound ATPase may be an important regulator of contractile function – particularly of contraction velocity (reviewed in [3]). Genesis of ATP is therefore crucial, in order to enable contraction, but also to maintain electrical integrity (through a Na + /K + -ATPase).

This myocardial contractile process is metabolically 'expensive' and its metabolic rate is thus extremely high. The human heart will utilise oxygen at a rate of 8 ml/100 g/min at rest and 50 ml/100 g/min during intense exercise or illness compared to 0.2 ml/min/100 g for resting skeletal muscle or just 0.4 ml/100 g/min for the whole human body [4]. The heart of an 80 kg resting man will thus use 5 % of the total body oxygen consumed – 80 % of which is used for the contractile process [5].

This oxygen is delivered through the coronary circulation.

In vivo, coronary autoregulation maintains constant flow over perfusion pressures of 60–140 mmHg so long as O2 demand is constant. The amplitude of this plateau is increased when myocardial oxygen use (MVO2) is higher [6]. The initial inflection point at the origin of the plateau is at higher pressure for subendocardial tissues, and coronary autoregulation capacity is also lower in the right than the left ventricles [7].

In vivo, of course, this autoregulatory capacity is masked. MVO2 is intensely supply dependent, because changes in substrate delivery (blood pressure and cardiac output) are inextricably linked to changes in cardiac loading conditions and work, and hence substrate demand.

This linkage of oxygen demand to supply has to be very tight indeed. The human myocardium is totally dependent on this oxygen supply, as it relies exclusively on aerobic metabolism and cannot incur significant oxygen debt. Myocardial tissue oxygen extraction (MEO2) cannot increase significantly from its basal level of < 70 % (compared to 25 % in most organs), and coronary vasodilatation is thus the only real way to allow for in-

creased myocardial oxygen utilisation (MVO2). Indeed, MVO2 and CBF are linearly-related [8]. Coronary resistance is equally divided between the vast myocardial capillary bed (500 cm^2 per gram of tissue: 4 times that of skeletal muscle) [9] and arterioles of < 100 microns diameter.

All of these vessels are under vasomotor control [10]. The difference between basal coronary flow (80 ml/min/100 g) and the maximum which can be pharmacologically induced is termed 'coronary flow reserve' and is very large: flows can increase through vasodilatation by an order of 4–6-fold.

With increasing cardiac work, coronary flow increases up to a maximum. Beyond this point, cardiac work becomes supply-dependent. At this point, contractility falls in order to maintain cardiac output at a sustainable level for a given level of oxygen consumption [4]. This situation may arise in conditions such as sepsis, especially if coronary disease is also present.

Means of increasing cardiac performance

The classically-described 'Starling Curves' relating ventricular end-diastolic pressures with stroke work have been replaced in the human by the concept of a 'family' of such curves, whose relative position and gradient is determined by the contractile state of the ventricle [11]. Studies by Braunwald in humans suggest that, under normal circumstances, the heart functions near the top of a Sarnoff curve [12, 13]. Nonetheless, in principle, stroke output is determined by preload, afterload, and myocardial contractility.

Limits to cardiac reserve

Exhaustion of cardiac reserve may be profoundly deleterious. Cardiac reserve will depend on:

a. The slope of the Sarnoff Curve and the ability to move up it (partly determined by ventricular compliance)
b. Which Sarnoff curve one is on and the capacity to move to a different curve (current compared to maximal inotropic response)
c. Where on the curve one already is (determined by loading conditions and compliance)

Each of these factors will also depend on a number of other factors including the balance between oxygen supply and delivery to the heart. Hence coronary reserve may play a crucial role, as may alterations in the metabolic efficiency of the myocardium.

Cardiac reserve in cardiac disease

Extravascular compressive forces proportional to afterload comprise 40% of coronary vascular resistance. These compressive forces (and hence coronary flow) are phasic: 80% of LV flow occurs in diastole. MVO2 is 20–40% higher in the subendo- than subepi-cardium, due to increased cell shortening and wall tension here. With increasing heart rate and afterload, time in diastole reduces and wall tension rises, thus reducing subendocardial flow at a time when metabolic demands are rising. The subendocardium thus reaches supply-dependency earlier than other regions of the ventricular wall.

In left and right ventricular (LV and RV) hypertrophy, capillary bed size is not increased. Thus, although flow per unit weight is normal at rest, there is already a degree of vasodilatation at work, and coronary flow reserve is less. In the normal thin-walled RV, compressive forces are minimal and coronary flow is little influenced by cardiac cycle. In RV hypertrophy, as well as in the normal LV, subendocardial flow is phasic, and the subendocardium again vulnerable to ischaemia [14]. Increased collagen matrix in cardiac hypertrophy reduces diastolic compliance and hence preload reserve (the recruitment of contractile reserve by changes in LVEDP mediated through sarcomere stretch). Thus, the hypertrophied ventricle is associated with limited preload reserve, lower coronary flow reserve (especially in the subendocardium) a 'flatter' Starling/Sarnoff curve, and reduced cardiac reserve.

Tension generated in the myocardium is inversely proportional to ventricular radius: big ventricles require greater tension to generate a given pressure, and consume more oxygen. The dilated LV therefore has lower cardiac reserve due to higher basal consumption.

The need for increased cardiac work to maintain adequate oxygen delivery in anaemic states leads to increased basal MVO2. At low haematocrits (approximately 12%, or a Hb of 3.5 g/dl) coronary flow reserve is exhausted. For similar reasons, hypoxaemia will also use up coronary flow reserve and cardiac 'work reserve', with a critical limit being an FiO2 of 12% acutely in dogs [15].

Finally, coronary arterial narrowing (due in general to coronary atherosclerosis) will also reduce coronary reserve, even to the point where flow-dependency of function is reached.

Cardiac reserve in sepsis

Myocardial dysfunction occurs early in sepsis [16]. LV ejection fraction often falls even in the absence of shock [17], although stroke volume may be maintained through an increase in end-diastolic volume [18]. Septic patients generally increase cardiac output with fluid

challenge, but through varied means: if end-diastolic volumes is initially low, Starlings Law operates, whilst if EDV is initially high, stroke volume increases through a reduction in afterload. Calvin found that fluid challenge had little effect on LVEDV or output in 30 % of patients, an effect ascribed to altered RV dynamics acting through ventricular interdependence [19]. In some patients, therefore, the Starling curve is depressed (being moved downwards and to the right) with reduced slope. In others, compliance is reduced in the ventricle. Thus, fluid challenges may increase LVEDP without increasing preload, or may increase preload without significant increase in cardiac work [20]. Such impaired cardiac reserve is associated with a poorer outcome [21, 22].

Specific factors influencing cardiac reserve in sepsis

Reductions in myocardial reserve may partly relate to:

(i) *Downregulation of myocardial beta- adrenoreceptor activity*, thus limiting inotropic and chronotropic responses and producing a downward shift of the Sarnoff curve [23, 24].

(ii) *Production of myocardial depressant factors*. Human blood from septic patients contains elements which depress myocardial performance [25]. Cytokines may play a key role, possibly through nitric oxide (NO). NO has a depressant action on cardiomyocytes [26] and is synthesised in cardiomyocytes by both a constitutive and inducible nitric oxide synthase (cNOS and iNOS respectively). Cytokines such as interleukin-6 (IL-6), IL-1, and TNF-alpha induce nitric oxide synthase in cardiac myocytes, causing a marked reduction in systolic performance [26, 27] through a cGMP-mediated mechanism [28]. In humans, a synergistic combination of IL-1beta and TNF-alpha may be especially important [29].

(iii) *Alterations in coronary blood flow* (CBF) may contribute to the myocardial dysfunction of sepsis. Coronary flow is higher in sepsis at any given work load [4] due possibly to inappropriate vasodilator release or reduced myocardial metabolic efficiency [30, 31]. Alternatively, oxygen extraction ratios may be reduced in sepsis in the coronary circulation, just as they may be in the systemic circulation [20]. This may reflect 'shunting', or impaired cellular O2 use. Whatever the cause, the ability to increase myocardial oxygen extraction is depressed [32] and coronary flow may be insufficient for the metabolic demands of the tissues, leading to depressed myocardial function.

(iv) *Altered cardiac metabolism*. Energy for cardiac contraction is mainly derived from oxidative phosphorylation. Lipid substrates are competitively preferred to glucose in the beating human heart [33]. In sepsis, metabolic alterations may impair myocardial performance through diverse mechanisms:

a. The heart may rely increasingly on endogenous metabolic substrates, whose depletion might therefore lead to impaired contractility [31]:
b. When myocardial oxygen delivery is reduced, glucose uptake initially increases dramatically. Glyceraldehyde-3-P dehydrogenase activity falls, however, limiting ATP formation from this source, and the generation of high levels of NADH and lactate cause further inhibition. An early increase in glycolysis is therefore followed by a fall. Increased sympathetic action, meanwhile, enhances free fatty acid production. These are used preferentially for metabolism – and yet require more oxygen for their metabolism than does glucose. They also further inhibit glycolytic flux. Thus, hypoxia (or reduced oxygen delivery) is detrimental to the metabolic efficiency of the heart.
c. Loading conditions alter metabolic efficiency. For a given external work, the heart pumps a larger volume at lower pressure more efficiently that a smaller volume at higher pressure [4]. Increased ventricular volumes (as seen in sepsis) also impair myocardial contractility.
d. Myocardial contractility influences MVO2 for any given external work: an increase in contractile state increases energy use during that contraction, and not at rest between contractions [34].
e. Cellular metabolic efficiency can be modulated in health and disease [35], a mechanism which may rely upon the use of nitric oxide as a second messenger [36, 37, 38]. This is true not only of peripheral tissues, but also of the myocardium [39]. Impaired metabolic efficiency might explain some of the abnormalities of cardiac function seen in sepsis [40].

Novel strategies

In the septic state, there may be defects not only in oxygen and substrate delivery by the heart, but also in their utilisation by peripheral tissues. Non-survival is associated with an impaired ability to increase oxygen delivery and an inability to increase oxygen extraction [22]. Accumulation of lactate in body tissues despite high oxygen deliveries may be due to shunting or extraction failure, or a failure of cellular utilisation (metabolic failure).

A new therapeutic strategy for the critically ill might aim to increase coronary flow, improve cardiac function,

and improve substrate uptake and metabolic efficiency in all tissues. Such an intervention might improve cardiac reserve and performance (aiding substrate delivery) as well as peripheral tissue metabolism.

Renin-angiotensin systems (RAS)

The circulating human renin-angiotensin system (RAS) plays an important role in circulatory homeostasis. Angiotensinogen produced by the liver is acted upon by renin (produced by the kidney) to produce angiotensin I (Ang I). This is cleaved by angiotensin converting enzyme (ACE), to generate the vasoconstrictor angiotensin II (Ang II). Ang II also stimulates adrenal aldosterone release (leading to salt and water retention), and degrades vasodilator kinins. In this way, increasing RAS activity raises blood pressure. However, local renin-angiotensin systems exist in diverse tissues including human myocardium [41], adipose tissue [42], and skeletal muscle [43].

RAS, coronary flow and diastolic function

ACE inhibition improves endothelium-dependent vasodilator responsiveness through a nitric oxide-mediated effect. It also reduce Ang II-induced oxidant stress within the vessels wall, and protect local nitric oxide from oxidative inactivation [44, 45]. ACE inhibition improves coronary flow through both stenotic and normal coronary arteries through a kinin-dependent mechanism [46]. These beneficial effects are likely to be mediated through local ACE inhibition rather than effects on circulating ACE [45]. In the hypertrophied heart, local (and not systemic) ACE inhibition may improve ventricular diastolic function and coronary flow reserve [45, 47, 48]. The effects of ACE inhibitors on reducing LV end-diastolic volumes may also be beneficial. Since myocardial wall tension is proportional to systolic ventricular pressure and inversely proportional to ventricular radius, vasodilatation and reduction in LVEDD through ACE inhibition may reduce myocardial work.

Metabolic effects of tissue RAS

Local RAS may influence tissue metabolic responses [43]. We have investigated this using a polymorphism of the human ACE gene in which the absence (Deletion, *D* allele) rather than the presence (Insertion, *I* allele) of a 287 base pair fragment is associated with higher tissue ACE activity [49].

Cardiac growth responses to exercise training were shown to be associated with the D allele [50]. Unpublished data suggested that this might be related to genotype-dependent differences in cardiac work for any given external work, with those of DD genotype performing more cardiac work per unit external work. The association of low ACE levels with improved biomechanical performance have since been substantiated [51]. The maximum time (seconds) for which 78 male recruits (mean ± SEM age 19.0 ± 0.2 years, height 176.6 ± 0.7 cm, body mass index 22.2 ± 0.2 kg/m^2) could perform repetitive elbow flexion whilst holding a 15 kg barbell was assessed both before and after the training period. Pretraining performance was independent of genotype (mean 119.8 ± 6.2 s). Duration of exercise improved significantly for those of II and ID genotype (79.4 ± 25.2 and 24.7 ± 8.8 s: p 0.005 and 0.007 respectively), but not for the 12 of DD genotype (7.1 ± 14.9 s: p 0.642). Improvement was thus eleven-fold greater (p 0.001) for those of II than DD genotype.

If these changes were due to enhanced efficiency of muscle metabolism, we might expect to see an allele skew amongst elite endurance athletes exercising at very high altitude – where calorie intake is low, calorie expenditure high, and oxygen supply low. 25 elite unrelated male British mountaineers with a history of ascents beyond 7000 m without the use of supplemental inspired oxygen were thus studied. Genotype distribution was compared to that of 1906 healthy British males. Mean (SD) age was 40.6 (6.5) years in the 25 subjects, and 55.6 (3.2) years amongst the 1906 controls. Both genotype distribution and allele frequency differed significantly between climbers and controls (p 0.02 and 0.003 respectively), with a relative excess of II genotype and deficiency of DD genotype [51].

If due to enhanced metabolic efficiency, we might also anticipate a relative conservation of energy stores to be associated with II genotype. We have demonstrated this to be the case [52]. At the start and end of training, assessment was made in 123 male army recruits of body composition using bioelectrical impedance, Magnetic Resonance Imaging of the mid-thigh, and multiple skinfold thickness measurements. Changes in body composition with training were strongly influenced by the presence of a D allele, and the relationship between changes in body composition in those with and without a D allele was similar across all three methods of assessment (Table 1).

Our observed genotype-dependent improvements in performance might in theory derive from increases in oxygen delivery (including cardiac output and muscle capillary density): conversion of type 2 to type 1 fibres of high oxidative capacity: and increases in mitochondrial numbers and density [53, 54]. They may also relate to a differential change in metabolic substrate: raised stress-hormone concentrations increase the availability of exogenous (carbohydrate and fatty acids from liver and adipose tissue) or endogenous (muscle triglyceride and glycogen stores) oxidative fuel [55], and endur-

Table 1 Mean changes in body composition with training, by ACE genotype

	n	Mean (SEM) change	p value (paired t test)	Adjusted mean change (± SEM)
Bioimpedance mass (kg)				
II	19	1.97 (0.57)	0.003	2.14
D +	61	–0.10 (0.60)	0.54	–0.1
				p value 0.001
Skinfold assessment: mass (kg)				
II	14	1.88 (0.69)	0.01	1.78
D +	13	–0.57 (0.51)	0.28	–0.47
				p value 0.01
MRI volume (cm^3)				
II	16	9.86 (2.51)	0.001	9.27
D +	14	0.15 (2.11)	0.98	0.83
				p value 0.01
FAT				
Bioimpedance fat mass (kg)				
II	19	0.73 (0.39)	0.07	0.55
D +	57	–0.26 (0.20)	0.21	–0.20
				p value 0.04
Skinfold assessment: fat mass (kg)				
II	14	–0.13 (0.33)	0.67	–0.36
D +	13	–1.66 (0.45)	0.004	–1.35
				p value 0.05
MRI fat volume (cm^3)				
II	16	0.59 (1.57)	0.70	0.16
D +	14	–3.34 (1.80)	0.08	–2.86
				p value 0.20
Bioimpedance non-fat mass (kg)				
II	19	1.09 (0.37)	0.007	1.31
D +	57	–0.08 (0.35)	0.82	–0.15
				p value 0.01
Skinfold assessment: non-fat mass (kg)				
II	14	2.01 (0.49)	0.002	2.00
D +	13	1.03 (0.34)	0.01	1.03
				p value 0.1
MRI muscle volume (cm^3)				
II	16	9.57 (1.80)	0.0001	9.32
D +	14	3.61 (1.25)	0.01	3.88
				p value 0.02

ance-trained individuals rely more heavily upon fatty acids as an energy source [56]. However, the association of increased body fat stores with improved physical performance might suggest an influence of ACE genotype on energy balance, and in the nature and efficiency of use of oxidative fuel for metabolism.

Such effects of ACE genotype on energy balance might be mediated through a number of different mechanisms.

Firstly, a local adipose RAS may alter substrate mobilisation. Angiotensinogen gene expression is high in fat and is influenced by nutritional state [57]. Both Ang II [57] and kinins [58] may exert a metabolic regulatory role. Kinins increase insulin-stimulated hexose transport in adipocytes [59], and ACE inhibition increases insulin suppression of nonesterified fatty acid flux [60].

Secondly, local RAS [43] may modify substrate utilisation. Skeletal muscle cells contain a complete kal-

likrein-kinin system [61]. The I allele is associated with lower kininase II (ACE) activity [49], and physical stress and hypoxia [62] raise skeletal muscle kinin levels [63, 64]. These in turn drive increased glucose uptake in exercise, and stimulate amino acid uptake [62]. Similarly, ACE-inhibition increases skeletal muscle glucose uptake, insulin sensitivity, glycogen storage, glucose transporter GLUT-4 synthase activity, hexokinase activity, and thus the adaptation of the enzymes responsible for glucose catabolism [65, 66]. Postoperatively, bradykinin increases forearm glucose uptake, and reduces both endogenous hepatic glucose production [67], and protein catabolism by ≤ 50 % [68]. Kinin-induced changes in blood flow [69] also play a role in improving glucose uptake through vasodilatation [70].

These renin-angiotensin system effects may work together with other metabolic tissues to influence whole body energy balance. Adipose and striated muscle GLUT4 glucose-transporter activity may be RAS-dependent, and can markedly alter whole body glucose disposal [71]. In rats, kinins may alter relative glucose/free fatty acid/beta-hydroxybutyrate substrate availability [68]. Angiotensin II has both gluconeogenic and glycogenolytic actions [72, 73], stimulates hepatic gluconeogenesis and shifts lactate uptake to release [74].

Finally, angiotensin II also causes wasting in rats partly through a metabolic effect [75], and increases glucose oxidation out of proportion to its uptake [76] suggesting inefficient utilisation. By modulating kinin levels, tissue ACE activity may also influence metabolic efficiency. Nitric oxide (NO) donors and bradykinin both reduce renal oxygen consumption, whilst inhibitors of NO synthesis reduce the metabolic efficiency of sodium transport [36]. Indeed, NO may be involved in the signalling processes which regulate muscle respiration [35].

Such effects on the efficiency of muscle mechanical function and energy utilisation may be of profound importance for the treatment of critically-ill patients. In the presence of ischaemia/reperfusion, both kinins and ACE inhibition preserve cardiac function and energy stores [77, 78]. ACE inhibition has been shown to modulate myocardial oxygen consumption [39], possibly through altering NO production [38].

Pulmonary effects of RAS

It would thus seem that human tissue metabolic performance might both be manipulated through local RAS activity. There may be other additional advantages. As discussed above, cardiac performance may be enhanced, leading per force to improved tissue oxygen delivery. Recent work at UCL also suggests that aspects of pulmonary function may additionally be improved. Data suggest that local lung RAS may be influencing ventilation/perfusion matching through the modulation of the hypoxic pulmonary vascular response. In addition, central respiratory drive may be under the control of neuronal RAS, whilst respiratory muscle function may be under RAS control in the same way as other skeletal muscle. Thus, RAS manipulation might be used to enhance both pulmonary and cardiac components of oxygen delivery, as well as improving its peripheral utilisation.

In conclusion

Impaired cardiac reserve is associated with a poorer outcome in the critically ill. Cardiac reserve varies with loading conditions, intrinsic cardiac disease, and inotropic status. It is also influenced by the balance between energy utilisation and delivery – in which coronary flow (and flow reserve) may play an important role.

In addition, metabolic efficiency of myocardial tissue will also influence cardiac reserve, and may interact with alterations in metabolic efficiency of peripheral tissues in sepsis to influence outcome: a failure of substrate delivery coupled with a failure of effective substrate utilisation is associated with a poorer outcome.

Recent data suggest potential novel roles for inhibitors of tissue renin-angiotensin systems in the critically ill. These may increase coronary flow, improve diastolic cardiac function, improve ventricular wall tensions and oxygen utilisation through biomechanical effects, alter substrate mobilisation, improve substrate uptake and improve efficiency of metabolic substrate use. These effects have potential benefit to both myocardial performance and peripheral tissue and organ function.

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