The Control of the Exercise Hyperpnoea

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Chapter 6

General Discussion

6.1 Experimental findings

6.1.1 Intermittent exercise

6.1.1.1 $\dot{V}_E$-$\dot{V}CO_2$ coupling

The intermittent study again demonstrated that the $\dot{V}_E$ response was appropriate to the metabolic demands imposed by the intensity domain rather than the absolute work-rate. This coupling of $\dot{V}_E$ to the metabolic demands, both $\dot{V}CO_2$ clearance and respiratory compensation when required, in the face of constant, presumably intense, central drive enforces the belief that a primary component of the respiratory control system must include a humoral element. Although, it should be pointed out that none of the exercise phases were sufficiently long enough for subjects to achieve a steady-state, therefore no conclusion can be drawn regarding the control of $\dot{V}_E$ during phase III.

The uncoupling of $\dot{V}_E$ from $\dot{V}CO_2$ during phase I of the off-transient is an interesting finding and warrants further investigation of the mechanistic basis of these changes in $\dot{V}_E$.

6.1.1.2 Isocapnic buffering

The partitioning of the exercise phase into varying time domains illustrated that the delayed onset of respiratory compensation was not strictly $[La^-]_a$ dependent nor related to the central drive. However, the results of this study cannot further elucidate the mechanisms underlying the delay. To further out understanding detailed knowledge of both the behaviour of the carotid bodies in response to the conditions typically associated with supra-$\hat{\theta}_L$ exercise, and the respiratory controllers response to such inputs might be required. This would begin to allow us to establish why there is delay in the onset of respiratory compensation while the carotid bodies have been shown to respond rapidly to the presence of metabolic acidosis (e.g. Biscoe *et al.*, 1970; Hornbein & Roos, 1963; Ponte & Purves, 1974).

6.1.2 LTM

6.1.2.1 Neural mechanisms underlying LTM

Recently some definitions of modulation and plasticity with regard to respiratory control have been proposed (Mitchell & Johnson, 2003). The term modulation has been defined as a neurochemical modification of synaptic strength over a relatively short time period, that is only active while the neuromodulator is present (e.g. 'STP' changes during an exercise trial) (Mitchell & Johnson, 2003). This is distinct from plasticity, which has been defined as a persistent change

within the neural control system which outlasts the stimulus (Mitchell & Johnson, 2003). However, while such standardisation should be welcomed, the terms used in this thesis reflect those in the literature to date and not these definitions. As such, short-term potentiation (STP) whether referred to here or by Eldridge for example is what is actually being defined as modulation; i.e. it is a short-term change which is reversible in the absence of the stimulus. Whereas long-term modulation (LTM) or long-term plasticity (LTP), while only LTM has been used during this thesis the terms appear interchangeably in the literature, both represent plasticity; i.e. neural changes based on experience that persist after removal of the stimulus. This can be schematised by figure 6.1.

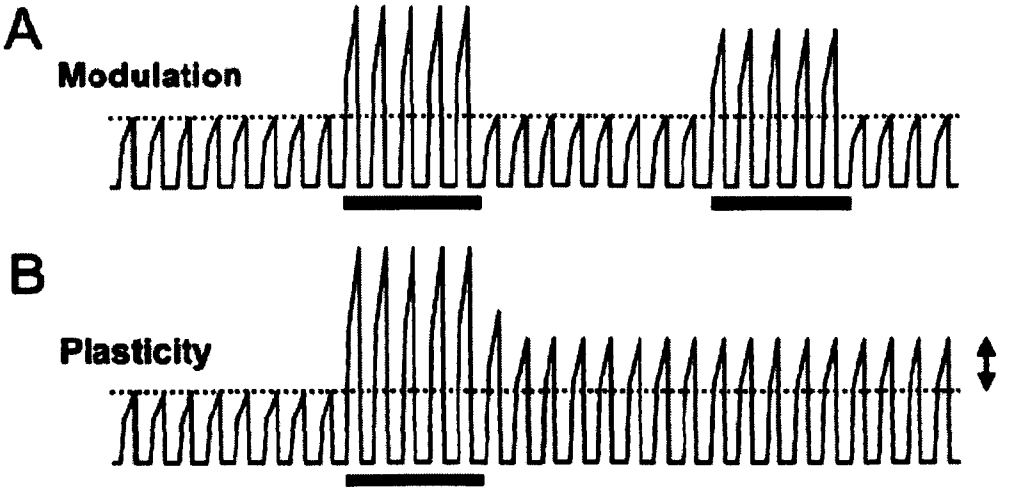

Figure 6.1: Schematic representation of modulation and plasticity. Panel A illustrates modulation, whereby an increased activity is seen in the integrated activity in the respiratory nerves while a neuromodulator (black bar) is present. This response does not persist when the neuromodulator is removed. Panel B illustrates plasticity, the same response is seen while the neuromodulator is present. However, when the neuromodulator is removed the response is a slow decline to an increased level (relative to baseline). Reproduced from Mitchell & Johnson, 2003.

While much is known about the mechanisms underlying certain types of respiratory plasticity (e.g. hypoxia induced, Bavis & Mitchell, 2003), little is known for certain about the structural basis of exercise induced plasticity. However, there are two demonstrations that are of particular importance. Firstly

that LTM in goats is abolished by para-cholorphenylalanine, a serotonin depleter (Johnson & Mitchell, 2001) and secondly that STP of the exercise hyperpnoea in goats also appears to be under serotonergic mediation (Bach *et al.*, 1993; McCrimmon *et al.*, 1995; Mitchell *et al.*, 1993; Mitchell *et al.*, 1995). Therefore, it appears that LTM may be operating via the same pathway as STP and as such may indicate a consolidation of the changes initiated by STP.

Furthermore, as both STP and LTM appear serotonin dependent it is likely that these forms of respiratory plasticity operate via neuromodulator (i.e. serotonin) induced changes in synaptic strength (see figure 6.1). That is to say that serotonin release onto the pre-synaptic terminal activates intra-cellular signalling molecules which initiate changes resulting in increases of synaptic strength. In the short term the activated kinases may bring about increases in synaptic strength through modulation of existing channels and receptors (e.g. by phosphorylation).

Further, more robust longer-term changes are proposed occur as repeated activation of serotonin receptors may bring about protein synthesis, possibly of kinases and neurotrophic factors for example, thus producing longer lasting plasticity (Mitchell & Johnson, 2003). It is hypothesised that hypercapnic exercise (i.e. during conditioning with increased V_D) increases activity in brainstem serotonergic raphae neurons which terminate in respiratory control regions. This increased activity results in increased serotonin release which may increase ventilatory output through increases in synaptic potency (Johnson & Mitchell, 2001).

6.1.2.2 Phase III

In the absence of any evidence of a role for LTM in the control of the phase II and III moderate exercise hyperpnoea, nor even any evidence of the existence of such a mechanism, how does this impact on the currently proposed control schemes? Even the strongest proponents of a humorally mediated control system do not seriously contend that chemoreception can account for the entire increased drive to breathe, above rest or a lower work-rate for that matter, during phase II and III. Additionally, essentially no one proposes a carotid or central chemoreceptor drive during phase I. Therefore, during each phase of the ventilatory response, regardless of the control scheme being proposed, classical neural mechanisms proportional to the exercise intensity seem likely to be operational.

With this specific frame of reference, could the system require a learned component during the phase II or III response? The neural drives, predominantly central command and muscle reflexes, that are purported to provide part of the increased drive to breathe are by definition proportional to the generation of muscular activity (central command) and proportional to muscular activity (muscle reflex). Therefore, while not able to generate a hyperpnoea proportional to CO_2 clearance, such mechanisms could provide a component of the total drive proportional to the work-rate. This would leave a constant proportion of the total drive across work-rates requiring to be provided by humoral mechanisms. This is consistent with the work of MacDonald *et al.* (1990) which showed a constant

proportional carotid body drive, a contribution of ~20%, independent of work-rate during phase III.

Therefore, in such a scheme, what advantage would a 'learned' response provide? At face value there would seem to be no advantage to a learned response over one simply proportional to muscular activity as described above. However, if the contributions of central command and muscle reflexes are to account for ~80% of the phase III hyperpnoea: How does the respiratory controller equate a given input from central and peripheral drives to an output equivalent to 80% of the total requirement? In such a model it would seem prudent to propose that a role for LTM might be to adjust the ventilatory output to the input from central and peripheral neurogenesis to the appropriate level, e.g. ~80% of the total requirement, allowing the humoral contribution to 'top-up' and create the proportionality between $\dot{V}_E$ and $\dot{V}CO_2$. However, the demonstration that the ventilatory response of 'cycling naïve' subjects is appropriate, despite presumably not 'learning' the match between central command and muscle reflex to the ~80% of the required drive seemingly precludes this. This could indicate redundancy within the system or that the efficiency of the carotid bodies at 'fine-tuning' the response requires only a crude approximate drive from central command or muscle reflex. Therefore, the system may not require plasticity to accurately match the central drive to a very accurate output. Alternatively, only coarse refinement of the input-output characteristic may be required, which could potentially be achieved without such a specific 'exercise-memory' as was hypothesised to be excluded in the study, i.e. the plasticity may occur during basic day-to-day exercise such as walking.

What is not clear, if the central command and muscle reflex drives are integrated in some way to provide ~80% of the total drive during phase III, i.e. they provide a drive proportional to ~80l/min if the total requirement is 100l/min, then why does ventilation not simply rise to this level, during phase I and II? Could the carotid bodies actually provide a constraint to $\dot{V}_E$ during phase II and cardio-dynamic mechanisms the same during phase I? The alternative would seem to be STP increasing the neural drive that originates during phase 1. However, how the 'on' 'off' asymmetry of STP when the stimulus is present versus not present is compatible with the 'on' 'off' symmetry of the ventilatory response irrespective of whether the stimulus is present during recovery (i.e. transition to rest) (e.g. Whipp *et al.*, 1982; Griffiths *et al.*, 1986).

6.1.2.3 Phase II

Can a similar role for a memory-related phenomenon be envisaged in phase II? The instinct here is to consider STP, i.e. reversible plasticity within the exercise bout, which has been shown to have an intrinsic time course not dissimilar to $\dot{V}_E$ during moderate exercise. Furthermore, in the absence of a sustained increased error signal capable of driving an increased carotid body contribution, could STP 'heighten' the carotid body drive despite an insufficient increase in the basic stimulus?

Firstly this would require a stimulus to trigger such a mechanism. There is likely to be a small transient hypercapnia during phase II as ventilation lags slightly

behind $\dot{V}CO_2$; i.e. is slightly low for the requirement. Could this small elevation in P_aCO_2, conventionally thought too small to actually mediate the phase II rise in $\dot{V}_E$, provide the trigger to STP of the carotid body input to the respiratory controller. As such, the small increase in P_aCO_2 which is sustained relatively constant and hence cannot provide the continually increasing drive needed for a classical humoral drive during phase II, would begin to increase $\dot{V}_E$ proportional to the error signal. Then, as P_aCO_2 stabilises and falls, i.e. the classical humoral drive is removed, potentiation of the signal could continue to increase the drive to breathe thus continuing the increase in $\dot{V}_E$.

The time course of STP in the absence of an input is quantitatively similar to that for $\dot{V}_E$, the rapid time course typically observed for the onset of STP is actually a composite of STP plus the stimulus. In such a scheme the proposed stimulus is likely to be greatest shortly after the switch from phase I to II and decline thereafter. The reduction in stimulus might allow the time course of the STP itself to be manifest and thus provide the slow drive to $\dot{V}_E$. However, how this could account for situations where experimental manipulation speeds or slows $\dot{V}CO_2$ kinetics, e.g. prior hyperventilation (see page 49), is unclear.

6.1.2.4 Phase I

As already discussed phase I is the most likely candidate to involve a role for LTM (see page 233). These studies are unable to shed any light on the issue and so further work is required. However, it is worth considering whether a similar

mechanism as discussed for phase III might be appropriate. That is, could LTM set the appropriate $\dot{V}_E$ in response to a given intensity of stimulus from central command, for example? This could be consistent with Beaver and Wasserman's demonstrations (1968 and 1970) that less experienced subjects exhibited less marked phase I responses. Could they simply not have learned the appropriate output ($\dot{V}_E$) in response to the input (e.g. central command)?

Therefore, while the studies conducted during this thesis find no role for, or evidence of, LTM in the phase II and III responses. Thus suggesting it is not a primary component of the control system; it is not possible to rule out plasticity within the controller being required in some way. One possibility being involvement in fine-tuning the input-output characteristics of the $\dot{V}_E$ response. Furthermore, a role during phase I has yet to be rigorously investigated and should a demonstration of LTM in phase I be made, it may clear up the uncertainties regarding the requirements of a conditioning paradigm. This would therefore allow re-evaluation of the LTM studies currently in the literature to be performed.

6.2 How is $\dot{V}_E$ controlled?

The simple and probably most commonly given answer to this question is that we do not know. However, this answer does not give credence to the amount of information amassed in the literature. The consequence of this however, is that there is not the scope to critically discuss every piece of information relating to the control of the exercise hyperpnoea with the aim of fitting them together and producing a complete picture. Even if this could be done there remains the possibility the final picture will be incomplete, as our knowledge almost certainly is. Therefore, certain demonstrations which have a major bearing on our ability to piece together the picture of a functional control scheme will be focused on; specifically those demonstrations that seem to preclude involvement of particular control mechanisms.

6.2.1 Phase I

Firstly the work of on spinal cord transected patients, predominantly the studies of Adams *et al.* (1984). The weight of existing evidence seemingly precludes conventional chemoreception from mediating the phase I response. Therefore, both the experimental evidence and the pattern of response are suggestive of a controller capable of 'seeing' changes immediately at exercise onset. It is worth noting that it is not the neural transmission time from carotid bodies to respiratory controller which rules them out, but their physical separation from

any changes observed with the onset of exercise. This leaves central command, muscle reflex and cardio-dynamic linkages.

Adams *et al.* (1984) show significant increases in both $\dot{V}_I$ and $\dot{V}CO_2$ with consequently stable $P_{ET}CO_2$ and R by the second breath after exercise onset, i.e. essentially normal responses. Although, it is worth noting that when exercise is initiated during expiration, changes are typically seen within that respiratory cycle (e.g. Whipp *et al.*, 1970). Exercise was initiated during expiration in the study in question, furthermore $\dot{V}_I$ rather than $\dot{V}_E$ was measured. Therefore it might have been expected that changes would have been seen in the first breath rather than the second. The subjects involved in the study had clinically complete thoracic level lesions and as such there could have been no involvement of a peripheral reflex, at least via the spinal cord anyway. The absence of central command was assumed and it was suggested to be the case as the subjects were said to often be unaware exercise was taking place.

Furthermore, utilising a similar exercise protocol Adams *et al.* (1987) compared the changes in cardiac output and $\dot{V}_I$ during voluntary and electrically induced exercise and found no specific relationship between the two. However, the study did not utilise paraplegic subjects.

How then can these seemingly inconsistent findings be brought together? The use of Positron Emission Tomography (PET) over the last decade has displayed an involvement of higher centres during exercise onset and offset (e.g. Fink *et al.*, 1995; Thornton *et al.*, 2001). Employment of such techniques during induced

exercise in spinal cord transected subjects should confirm whether central command was absent during the studies of Adams *et al.* and others. Clearly if the outcome of such a study was to show increased activation of the motor cortical areas thought to be important in central command in tandem with a typical phase I response. Alongside no correlation between $\dot{V}_E$ and $\dot{Q}$ then it might be a significant step closer to allowing a conclusion that the Phase I response is driven by central command. However, if no activation and hence no central command could be demonstrated, but still a 'normal' phase I response, then either central command is not involved in phase I or is not required for phase I.

There is, I believe, sufficient evidence in the literature to promote the latter consideration as the more plausible. Regardless, the position in the literature at the moment does not allow a distinction between the system exhibiting hierarchical redundancy or experimental error. To conclude if central command is the predominant mediator of phase I one of two demonstrations is required. Firstly whether or not central command is actually present in spinal cord transected subjects exhibiting a 'normal' phase I $\dot{V}_E$, or secondly a demonstration that spinal cord transected subjects, without any volitional attempt to generate exercise, do not normally increase $\dot{V}_E$ during phase I. Either a positive outcome in the former or a negative outcome in the latter would suggest that the increases reported in the literature are actually unrelated to a normal exercise drive or reflect an attempt to generate motion. However, neither demonstration has been reliably made, therefore it is not possible at this stage to conclude on the specific pathways involved in phase I.

6.2.2 Phase II

While it is important to remember Eldridge's (1977) note of caution that a slow response does not necessitate a humoral one, especially given the rapid response typically exhibited by the carotid bodies, how a feedforward controller could be capable of directing the tight regulation between $\dot{V}_E$ and $\dot{V}CO_2$ is unclear. Equally, for that matter, a feedback controller unaware of the CO_2 clearance requirement, e.g. a muscle reflex mediated by group III and IV afferents. Even if the group III and IV afferents are capable of transducing information regarding CO_2 production, it is not obvious how they could be aware of the degree of CO_2 storage and hence the remaining volume of CO_2 requiring to be cleared. Therefore, the only mechanism seemingly capable of sensing the required information to match $\dot{V}_E$ to $\dot{V}CO_2$ during the dynamic phase is peripheral chemoreception.

There are many demonstrations in the literature supporting a role for the carotid bodies in phase II, many of which have already been discussed. Therefore I wish to focus principally on some interesting abnormalities in results and omissions from our knowledge. Oren *et al.* (1982) demonstrate that augmenting the carotid body drive, through chronic metabolic acidosis, speeds the $\dot{V}_E$ kinetics relative to $\dot{V}CO_2$, an effect which is seemingly abolished by hyperoxia. However, while hyperoxia slows the ventilatory kinetics in acidosis, alkalosis and control to essentially the same levels (roughly half as slow as for room air control, i.e. 'normal') it also slows $\tau\dot{V}CO_2$. Thus meaning that, under control conditions (with regard to acid-base status) in hyperoxia the same relationship exists

between $\tau\dot{V}CO_2$ and $\tau\dot{V}_E$ as in normoxia. This is in direct contrast to a carotid body mediation of the phase II hyperpnoea, as removal of the sensor (the carotid bodies through hyperoxic desensitisation) should uncouple the output response ($\tau\dot{V}_E$) from its input or target ($\tau\dot{V}CO_2$), i.e. not the case in this study. However, Griffiths *et al.* (1986) have demonstrated a separation of $\tau\dot{V}_E$ from $\tau\dot{V}CO_2$ with hyperoxia.

A possible demonstration to resolve this issue would be to examine the effect of manipulation of the body CO_2 stores (e.g. Ward *et al.*, 1983) prior to exercise with high F_IO_2. This should differentiate between the coupling of $\dot{V}CO_2$ to $\dot{V}_E$ during hyperoxia (Oren *et al.*, 1982) being coincidental or controlled by a structure other than the carotid bodies.

Another note of caution lies in regard to the interpretation of the slope of the $\dot{V}_E$-$\dot{V}CO_2$ relationship. This typically has a value of around 25 (e.g. Neder *et al.*, 2001). Therefore, it seems common practice to simply accept that the existence of a slope around this means that $\dot{V}_E$ has been appropriately controlled to accurately regulate P_aCO_2. However, this is not necessarily the case. For example, it has been reported that SCI subjects have a normal $\dot{V}_E$-$\dot{V}CO_2$ relationship (e.g. Adams *et al.*, 1982). However, SCI subjects typically have a reduced cardiac output during exercise (e.g. Jacobs *et al.*, 2002). Therefore, it is likely that pulmonary perfusion is compromised in these individuals; thus potentially reducing the physiological dead space less and requiring an elevated

$\dot{V}_E$ with respect to $\dot{V}CO_2$, i.e. a steeper $\dot{V}_E$-$\dot{V}CO_2$ relationship than normal (see page 28).

Furthermore, the 'noise' typically seen on the $\dot{V}_E$-$\dot{V}CO_2$ relationship (see results) hints at the possibility of P_aCO_2 fluctuating with this variability. How much P_aCO_2 fluctuates and whether this variability has sufficiently defined response characteristics to be capable of providing a stimulus the carotid body chemoreceptors remains to be elucidated.

Therefore, while the carotid bodies appear to be the predominant candidate to mediate the phase II hyperpnoea there are still some uncertainties. What is even less clear is exactly how the carotid bodies might sense the appropriate requirement, with regard to CO_2 clearance, for $\dot{V}_E$ at any given moment. There is no convincing evidence of an appropriate signal in mean P_aCO_2, the oscillation in P_aCO_2 or pH_a, the 'phase-coupling' of the oscillation, $[K^+]$ or any other known carotid body stimulant. Furthermore, it is not obvious how any stimulant not directly CO_2 related could provide the necessary information regarding the CO_2 clearance requirement.

The identification of a signal the carotid bodies are capable of transducing into an appropriate drive for $\dot{V}_E$ should be the next experimental goal. Consequently such a demonstration would also surely confirm that the carotid bodies are the mediator of the phase II hyperpnoea.

6.2.3 Phase III

There are few realistic voices denouncing a role for the carotid bodies in phase III. It is widely accepted that they contribute to ~20% of the total drive (Dejours test estimate, see page 60). The same concerns apply as during phase II regarding the source of their error signal. However, potentially of more interest is the remaining 80%; given the demonstration that SCI subjects exhibit a 'normal', with regard to $\dot{V}CO_2$, phase III ventilatory response despite the lack of a traditional muscle reflex and central command. While it is arguable that some volitional attempt to generate exercise despite the actual inability to do some may contaminate the phase I responses, it is unlikely that such subjects could continually provide the appropriate central drive while not actually generating exercise and therefore having no mechanical feedback. Therefore, where did the remaining 80% of the drive come from in such subjects?

Again hyperoxia may help elucidate the mechanisms. Should SCI subjects exhibit a greater decline than ~20% when breathing hyperoxia in the steady-state then the carotid bodies are increasing their contribution, with regard to 'normals'. This is quite plausible as the pattern of fibre type recruitment is typically reversed during electrically induced exercise and consequently the subjects are likely to be acidotic, which may augment the carotid body drive. Such a result would suggest it is still likely that a combination of muscle reflex drive and central command normally provide the majority of the 80% of the phase III drive not under carotid body mediation. However, if no greater that a 20% decrease is observed, taking care to ensure that the decline is not prematurely abolished by

corrective adjustments (e.g. error detection by central chemoreceptors), then it would seem likely that another mechanism must account for the remaining phase III drive.

Therefore, it would seem that two specific pieces of information are required regarding phase III. Firstly, what is the specific combination of mechanisms that provide the non-carotid body mediated drive? Secondly, similar to phase II (and potentially the same answer) what is the error signal detected by the carotid bodies in order to 'fine-tune' the ventilatory response?

6.2.4 Summary

To summarise, during phase I the weight of evidence in the literature seems to support a centrally located feedforward controller (e.g. central command hypothesis) despite some demonstrations to the contrary. Such a controller should be capable of creating the proportionality between $\dot{V}_E$ and $\dot{Q}$ through parallel activation.

The carotid bodies must almost certainly be involved in the control of phase II. An as yet unknown model of chemoreception seems the only plausible alternative mechanism and given the failure to demonstrate the existence of venous or pulmonary chemoreceptors, despite extensive searching, this seems unlikely. How the peripheral chemoreceptors receive the necessary information to provide the appropriate drive is as yet unclear.

The control of phase III is widely agreed to involve a contribution rather than mediation from the carotid bodies, the question of interest therefore remains how is the remaining contribution provided? The most plausible is probably a combination of all other feedforward and feedback structures, i.e. an integration of the drive arising from central command, muscle reflex and cardio-dynamic drive. The relation of central drive, and potentially all other inputs, to $\dot{V}_E$ especially during phase I and phase III seems the most likely mechanism to require plasticity or 'learning'. However, several experimental demonstrations are required to begin clearing up many of the reports conflicting with this hypothesis before these suggestions could be taken as a conclusion.

6.2.5 Supra-$\hat{\theta}_L$

The delayed onset of respiratory compensation typically seen in rapidly incrementing ramps does not appear to be related to a threshold in the $[La^-]_a$, although the degree of hyperventilation is related to the $[La^-]_a$. As the onset of respiratory compensation was delayed relative to the onset of exercise, the onset of metabolic acidosis and the transit delay of the acidosis reaching the carotid bodies it is unclear exactly what is mediating this time dependent delay. Although it appears not strictly concentration dependent it is possible that a threshold number of excitatory inputs is required by the respiratory control centres, presumably from the carotid bodies sensing the acidosis, before respiratory compensation is invoked.

6.3 Conclusions

While there was some evidence of the capacity for plasticity within the respiratory control system during trials with additional external dead space, no evidence could be found of a role for plasticity within the moderate-intensity ($<\hat{\theta}_L$) cycle ergometry hyperpnoea. A 'learned' response was not evident in either the phase II or phase III hyperpnoea following conditioning to moderate intensity cycle ergometry with added external dead space. Furthermore, the exercise hyperpnoea was essentially 'normal', with regard to arterial blood gas and acid base regulation, in subjects lacking in exercise experience and presumed therefore to be lacking in a specific 'learned response' to that mode and intensity of exercise. Therefore, while the respiratory control may exhibit the potential for plasticity, there appears to be no direct role for it in the control of the exercise hyperpnoea. Consequently no further conclusions regarding the potential control schemes proposed throughout this thesis can be drawn on the basis of these experimental demonstrations.

The onset of compensatory hyperventilation is delayed relative to the onset of exercise and of the acidosis. The delay does not appear to be related to a threshold level of acidosis, but the level of hyperventilation does appear to be linked to the degree of acidaemia. The results of this study cannot further elucidate the mechanisms which may be involved.

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Appendix 2.1

CENTRE FOR EXERCISE SCIENCE AND MEDICINE

MEDICAL HISTORY

(CONFIDENTIAL)

Please read.

It is important to take a record of your medical history. You may have, or may have once had a condition that would make this type of testing unsuitable for you. For this reason we ask you to be as truthful and detailed as possible. At no point will this information be made available to any one other than the principal investigators for this study. If you have any doubts or questions, please ask.

SUBJECT DETAILS:

NAME:

AGE: D.O.B:

SEX (M/F):

GP NAME & ADDRESS:

SMOKING:

Never Smoked .....
Not for >6 months .....
Smoke <10 per day .....
Smoke >10 per day .....

ILLNESSES:

ALLERGIES:

HOSPITALISATIONS:

MUSCULO-SKELETAL DISORDER:
(Arthritis, Joint Pain, Fractures, Sports injury, Others)

CARDIOVASCULAR DISORDER: (Fever, Heart Murmurs, Chest Pain, Palpitations, High Blood Pressure, Others)

RESPIRATORY DISORDER: (Asthma, SOB, Cough, URTI, Others)

GASTROINTESTINAL DISORDER: (Jaundice, Bleeding, Others)

DIABETES:

CNS DISORDER: (Fits, Blackouts, Tremor, Paralysis, Epilepsy, Other)

PSYCHIATRIC TREATMENT:

FAMILY HISTORY: (Sudden death in a first degree relative under the age of 35 years)

ARE YOU CURRENTLY TAKING ANY MEDICATION? No / Yes*

(*Please specify)_____

ARE YOU CURRENTLY TAKING ANY SUBSTANCES TO HELP IMPROVE YOUR TRAINING OR CONTROL YOUR WEIGHT i.e. CREATINE, PROTEIN SUPPLEMENT? No / Yes*

(*Please specify) _____

ARE YOU CURRENTLY TAKING ANY OTHER SUPPLEMENTS i.e. FOOD SUPPLEMENTS, VITAMINS? No / Yes*

(*Please specify) _____

CAN YOU THINK OF ANY OTHER REASON WHY YOU SHOULD NOT TAKE PART IN ANY OF OUR TESTS?

_____

SYMPTOMS:

Do you experience any of the following, particularly on exercise?

Breathlessness	No / Yes
Chest Pain	No / Yes
Dizzy Fits/Fainting	No / Yes
Palpitations	No / Yes

Please note that if you feel unwell on the day of the proposed test, or have been feeling poorly over the preceding day or two, please inform the investigators and DO NOT TAKE PART in the exercise test.

DECLARATION:

I have completed this questionnaire fully and truthfully. I have not kept any information from the investigators that may put myself at risk during high-intensity exercise, or affect the results that they obtain. I understand that I may withdraw from any one test or the study as a whole if I feel unwell, or feel uncomfortable with any part of the testing procedure.

(Signature).....

(Date) .....

PHYSICAL EXAM:

WEIGHT: _____ HEIGHT: _____

PULSE (Resting): _____ BP (Resting): _____

Screened by: .....

(Signature) ..... (Date) .....

Appendix 2.2

CENTRE FOR EXERCISE SCIENCE AND MEDICINE

ACTIVITY QUESTIONNAIRE

NAME: **SUBJECT NO:**

What kind(s) of exercise do you regularly do (20+ min/session)? (Please circle.)

	Number of times per average week.				
Walking	1	2	3	4	5
Running	1	2	3	4	5
Cycling	1	2	3	4	5
Swimming	1	2	3	4	5
Skiing	1	2	3	4	5
Rowing	1	2	3	4	5
Gymnastics	1	2	3	4	5
Martial arts	1	2	3	4	5
Tune up	1	2	3	4	5
Popmobility	1	2	3	4	5
Sweat session	1	2	3	4	5
Weight training	1	2	3	4	5
Field athletics	1	2	3	4	5
Racket Sports	1	2	3	4	5
Rugby/soccer/hockey	1	2	3	4	5
Other (s) *	1	2	3	4	5

*(Specify) .....

How long have you been exercising at least twice/week for at least 20 min/session?

(Signature) .....

(Date) .....

Appendix 3.1

INFORMATION SHEET

Physiological determinants of performance for intermittent dynamic exercise

You are invited to take part in a study involving exercise. We wish to describe how the body responds to exercise that lasts for a relatively long period (eg. 30 minutes) with intermittent exercise (ie. repeated short bursts of exercise that are interspersed with short recovery periods, lasting a similar period of time). Sports such as soccer and squash involve a lot of intermittent exercise, and we would like to improve our understanding of how the body adapts to this. We will therefore measure the responses of your breathing system, your heart and your muscles and also how you feel during these two kinds of exercise.

Testing will take place in the West Medical Building at Glasgow University. You are asked to take part in the following tests:

Progressive Exercise Test:
We will ask you to perform a "progressive" test on an exercise cycle, in which we would like to exercise until you can no longer continue (typically because your legs will become tired). This test will take about 15-20 minutes. The results of this test will allow us to estimate the maximal rate at which your body can take in and consume oxygen (an important "marker" of performance). On a previous occasion, we would like you to attend for a short a familiarisation trial. Also, you will have a short warm-up immediately before the test, and a warm-down immediately after the test.

Sustained Exercise Tests and Intermittent Exercise Tests:
On separate days, we will ask you to complete two "sustained" (or constant-load) submaximal exercise tests, to provide us with "control" responses: one will be at a moderate effort and the other at a higher effort. Each test will last no longer than 30 minutes. On other days, you will be asked to complete a 30-minute period of "intermittent" exercise, in which each exercise period will last between 0.5 and 10 minutes, and the intervening recovery periods will be of similar duration. This will allow us to compare the response to the intermittent exercise with those of the "control" tests. All tests will be preceded by a warm-up and followed by a warm-down.

Cardiovascular Measurements
We will monitor the rate at which your heart beats and its electrical activity, using mildly adhesive electrodes attached to the surface of your chest (electrocardiography).

Respired Air Measurements:
We will monitor the air that you breathe in and out so that we can calculate the level at which you are breathing and the amount of oxygen that enters your lungs and, we assume,

goes to your muscles. To do this, you will be required to breathe normally through a snorkel-type rubber mouthpiece to which is attached an integral monitor for sensing air flow, whilst wearing a nose clip (so that we can "capture" all the gas you breathe). A small fraction of the air will be sampled continuously by analysers for oxygen, carbon dioxide and nitrogen.

Perceptions of Breathlessness and Exertion:
At intervals throughout the tests, we will ask you to assess how breathless you feel and also how tired your legs feel, using a standard rating scale (e.g. with a range of numbers with word anchors to help you characterise the intensity of the sensations).

Noninvasive Measurement of Oxygen Levels in Blood:
The levels of oxygen in your blood will be measured noninvasively at one of your fingers or at an ear lobe (pulse oximetry), using a lightly-sprung "collar" that attaches to the measuring site. This involves a low intensity infra-red light (which is absorbed by haemoglobin - the oxygen-carrying pigment in your blood) being shone through the measuring site.

Noninvasive Measurement of Oxygen Levels in Muscle:
The levels of oxygen in the blood vessels of a part of your thigh muscle (quadriceps femoris) will be measured non-invasively (near infra-red spectroscopy). This involves a low intensity infra-red light (which is absorbed by haemoglobin). This will involve attaching the light transmitter and receiver to the surface of your thigh muscle with mildly adhesive tape.

Measurement of Lactate in Capillary Blood:
We will take capillary blood samples by pinprick sampling on a number of occasions during the tests so that we can measure the levels of a blood chemical called lactate, which is produced by exercising muscles when they start to fatigue.

Before you become a subject, you will complete a medical questionnaire. People who have asthma, heart related and/or circulatory problems, hypertension or any other contraindicated condition will not be allowed to take part in the study.

All information obtained both from the preliminary medical questionnaire and from the study itself will be treated confidentially. It is our intention to publish the results of this study, but not in a way which will not enable individuals or their performance to be identified.

You are free to leave the study at any time. The outcome of the study may not benefit you directly. Some parts of the study constitute a **possible transient risk to your health**. There is a **small cardiac risk** to your health. You may feel **uncomfortable** during certain stages of the tests. If you are **pregnant** or **may be pregnant**, you should not take part in the study.

Individuals who do not have an exercise science background may find some of the above terminology difficult to understand. Please ask one of the experimenters to **explain** any aspect which is unclear before you make your final decision about taking part in the study.

Consent Form

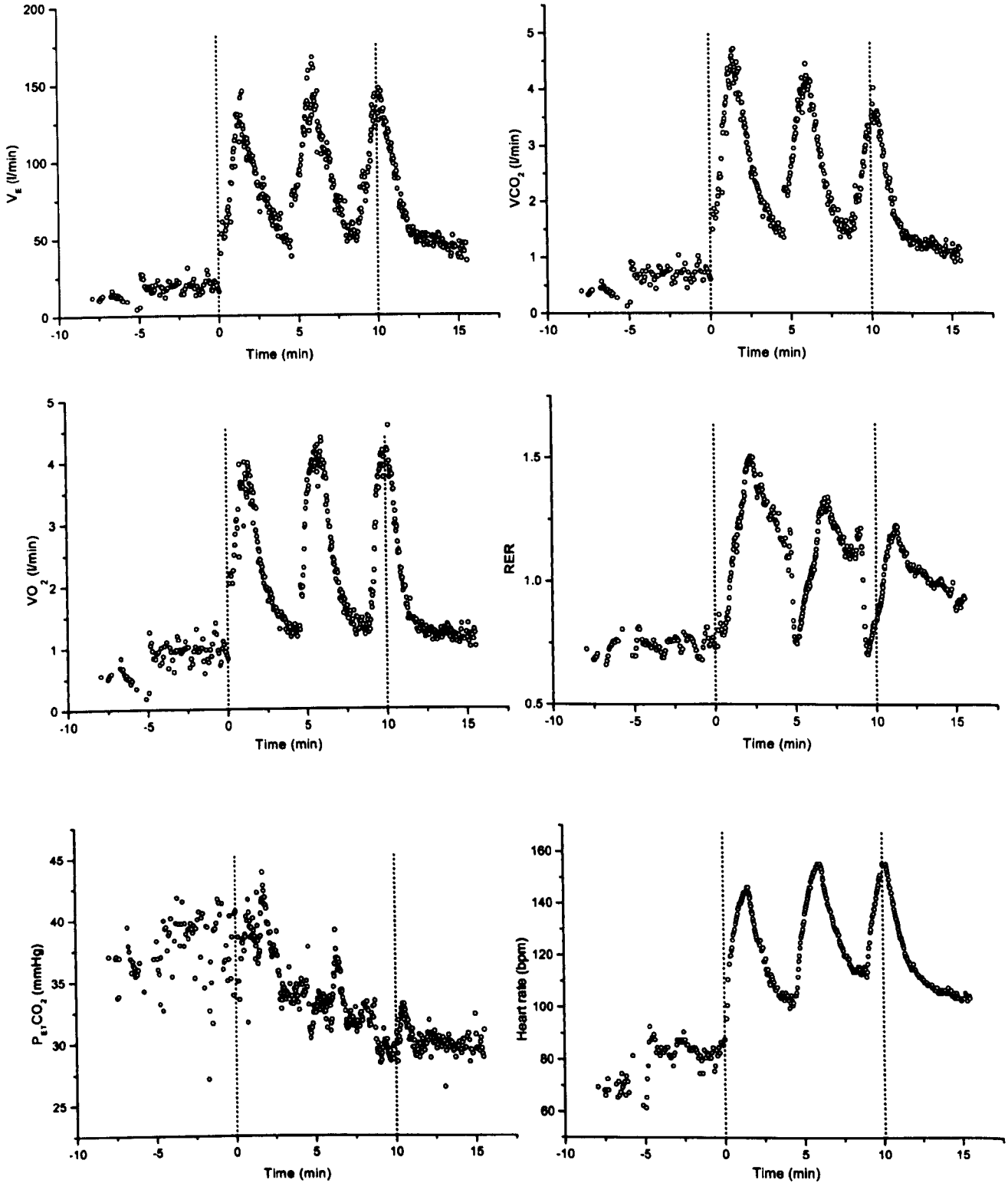
I,.....(PRINT)

of.....

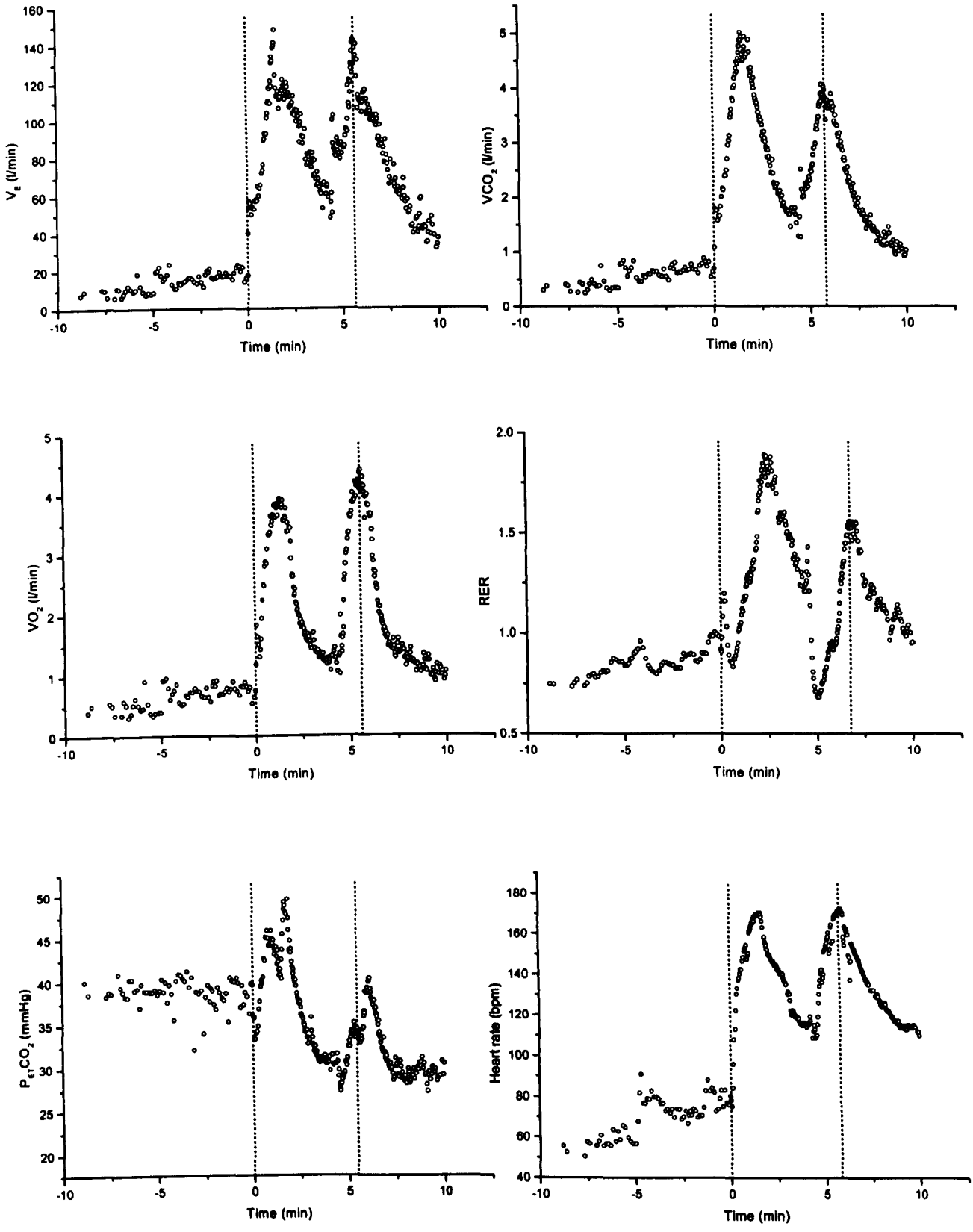
give my consent to the research procedures which are outlined above, the aim, procedures and possible consequences of which have been outlined to me

by.....

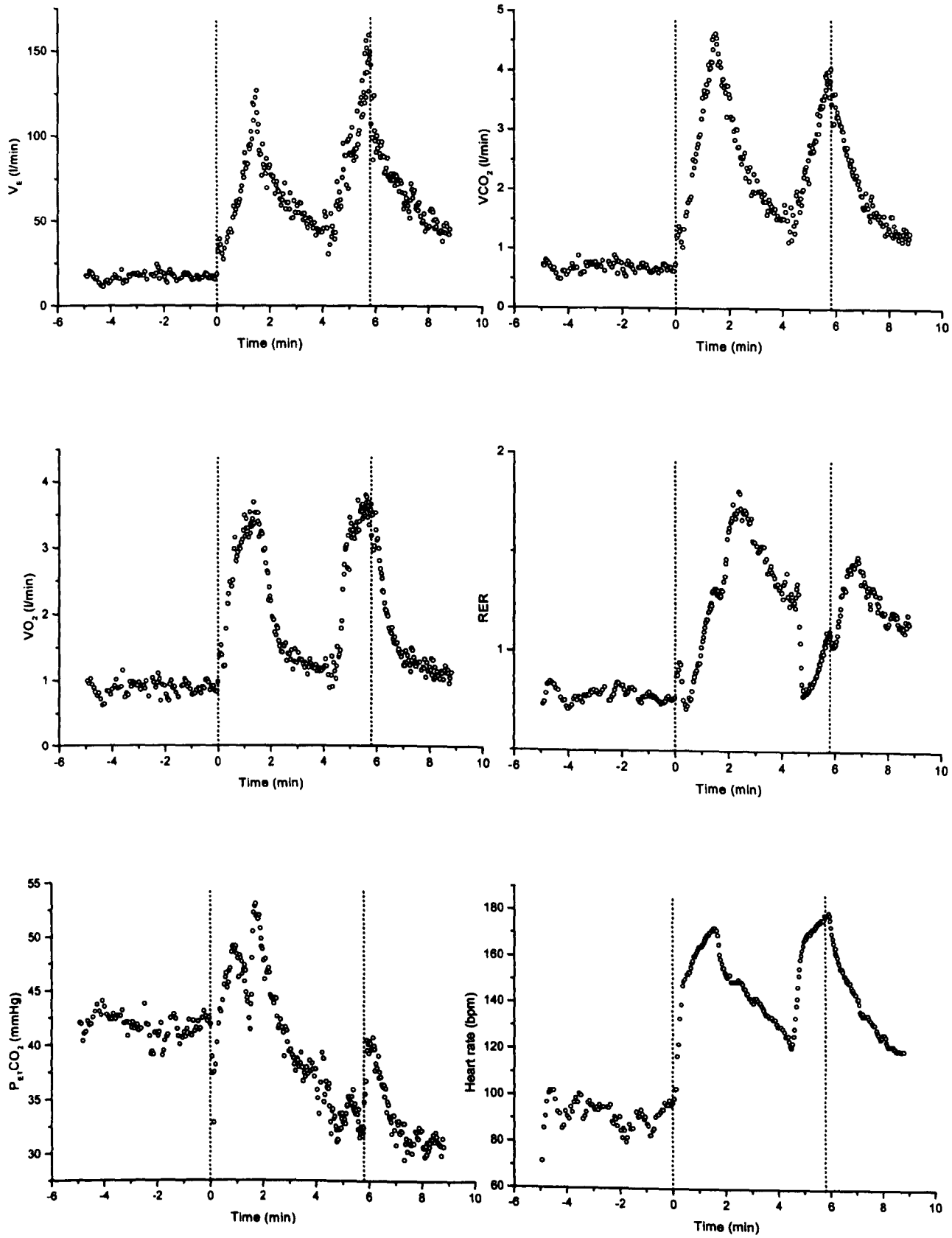
Signature.....Date.....



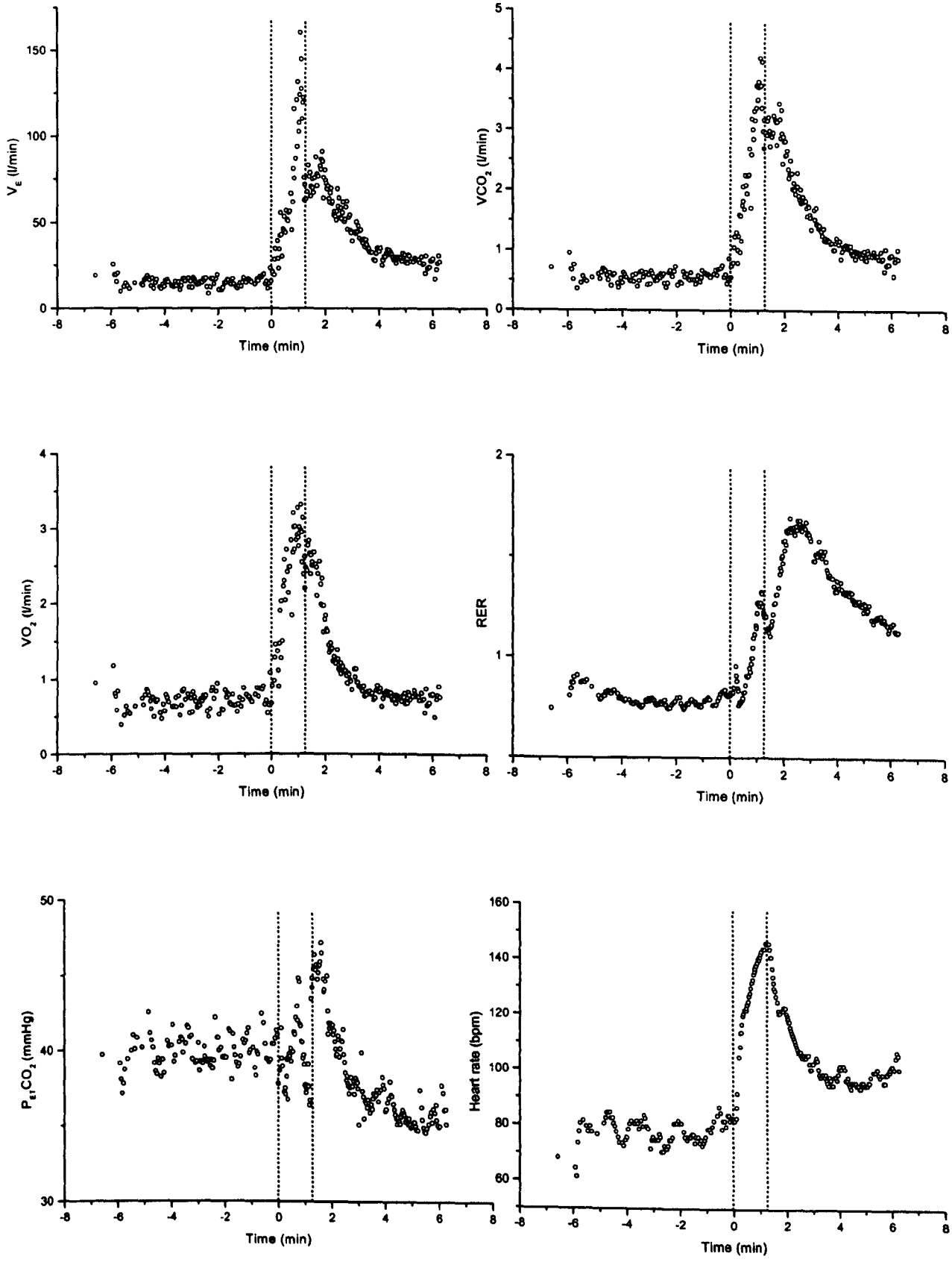
Appendix 3.2: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 1 during a 90s:180s intermittent exercise test. The vertical dashed lines indicate the beginning and the premature end of the thirty-minute period of intermittent exercise.



Appendix 3.3: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 3 during a 90s:180s intermittent exercise test. The vertical dashed lines indicate the beginning and the premature end of the thirty-minute period of intermittent exercise.

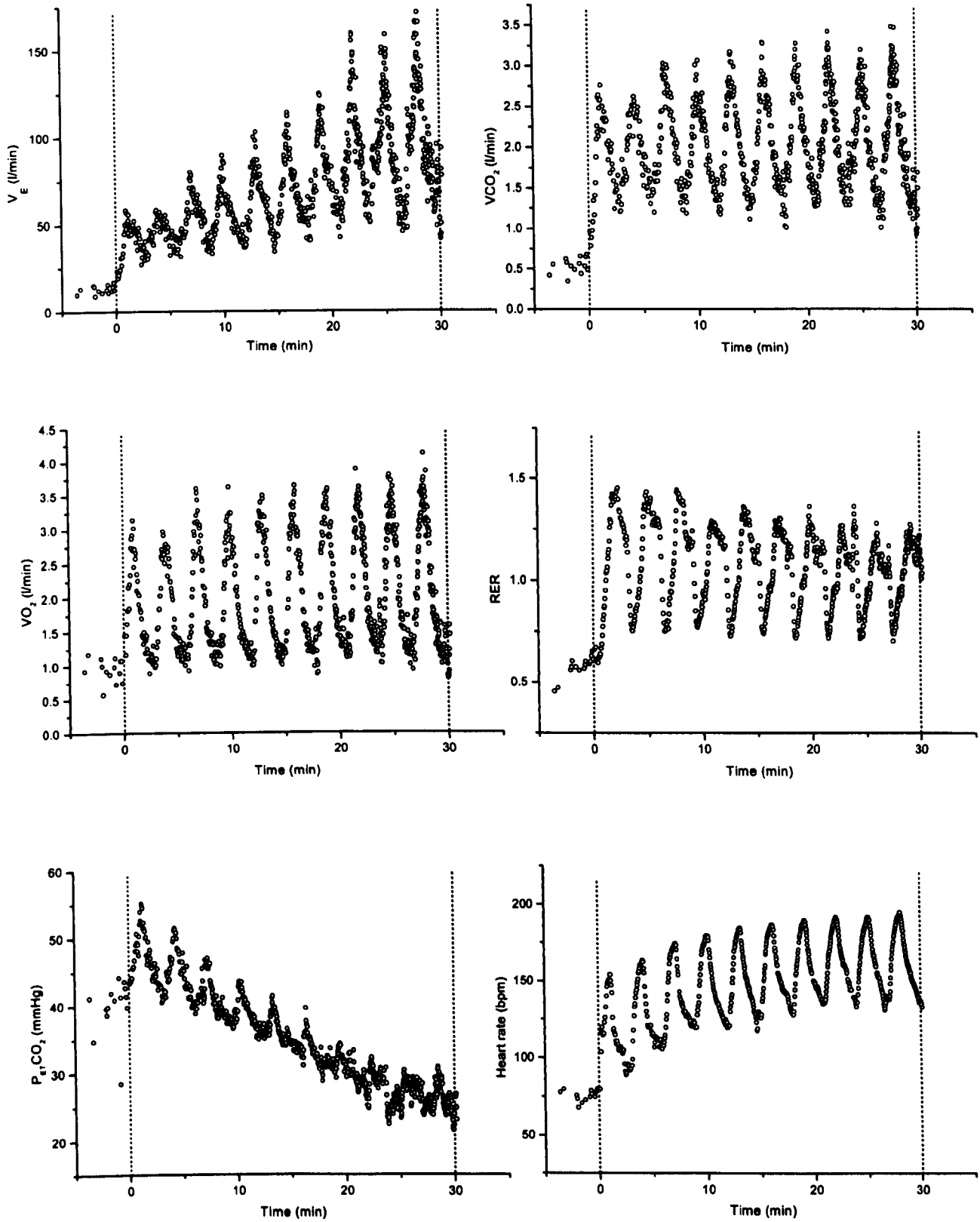


Appendix 3.4: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 5 during a 90s:180s intermittent exercise test. The vertical dashed lines indicate the beginning and the premature end of the thirty-minute period of intermittent exercise.

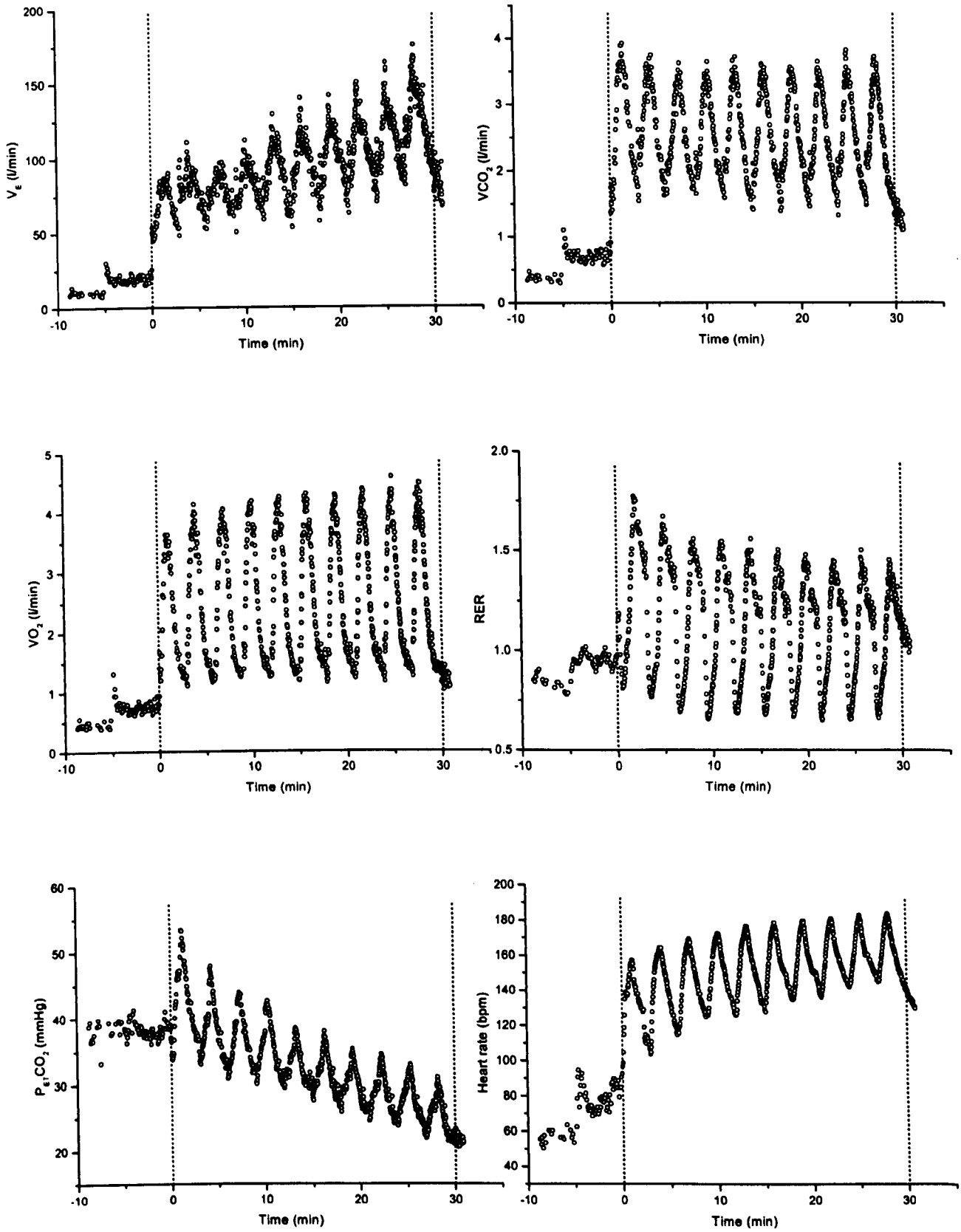


Appendix 3.5: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 6 during a 90s:180s intermittent exercise test. The vertical dashed lines indicate the beginning and the premature end of the thirty-minute period of intermittent exercise.

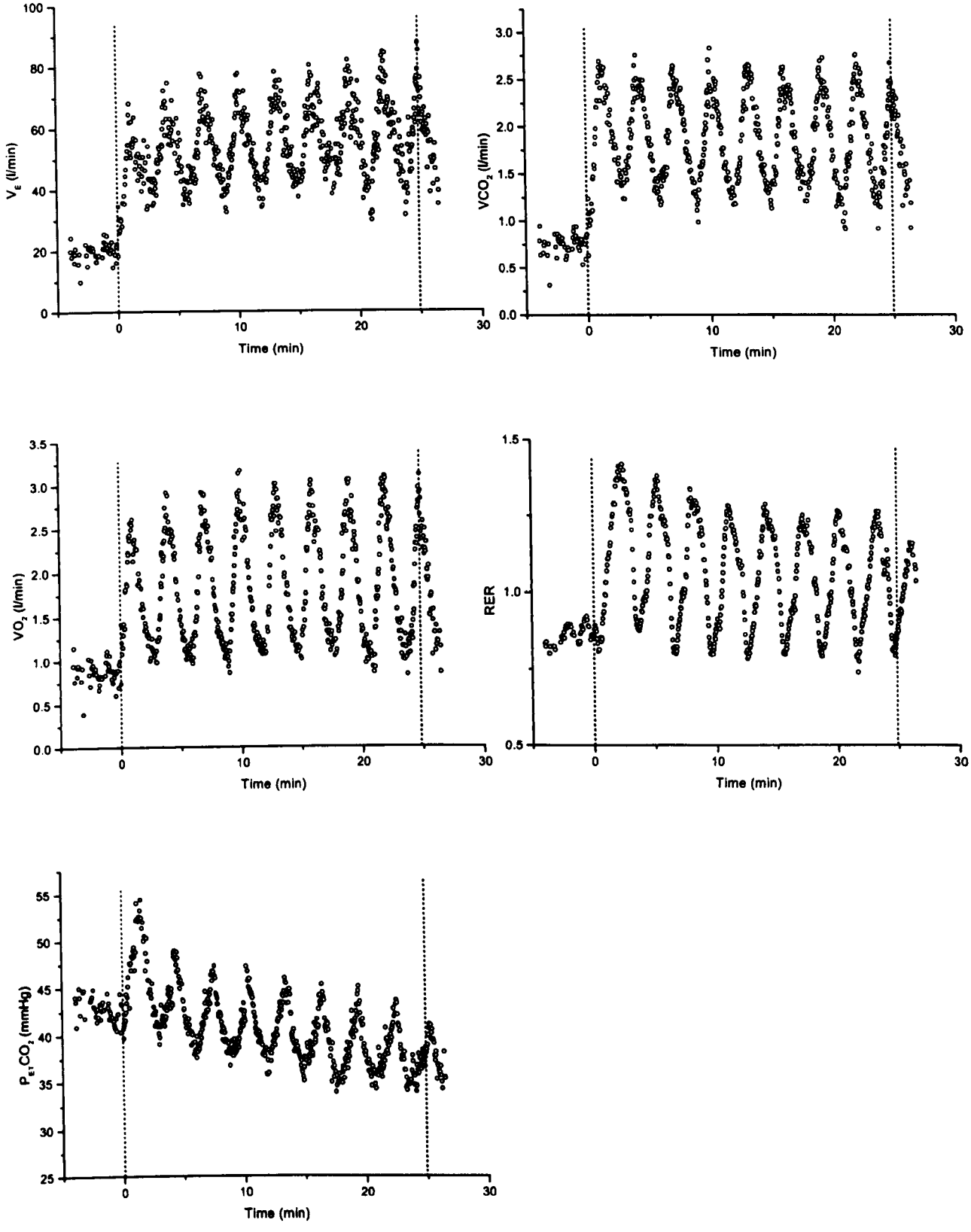
Appendix 3.3



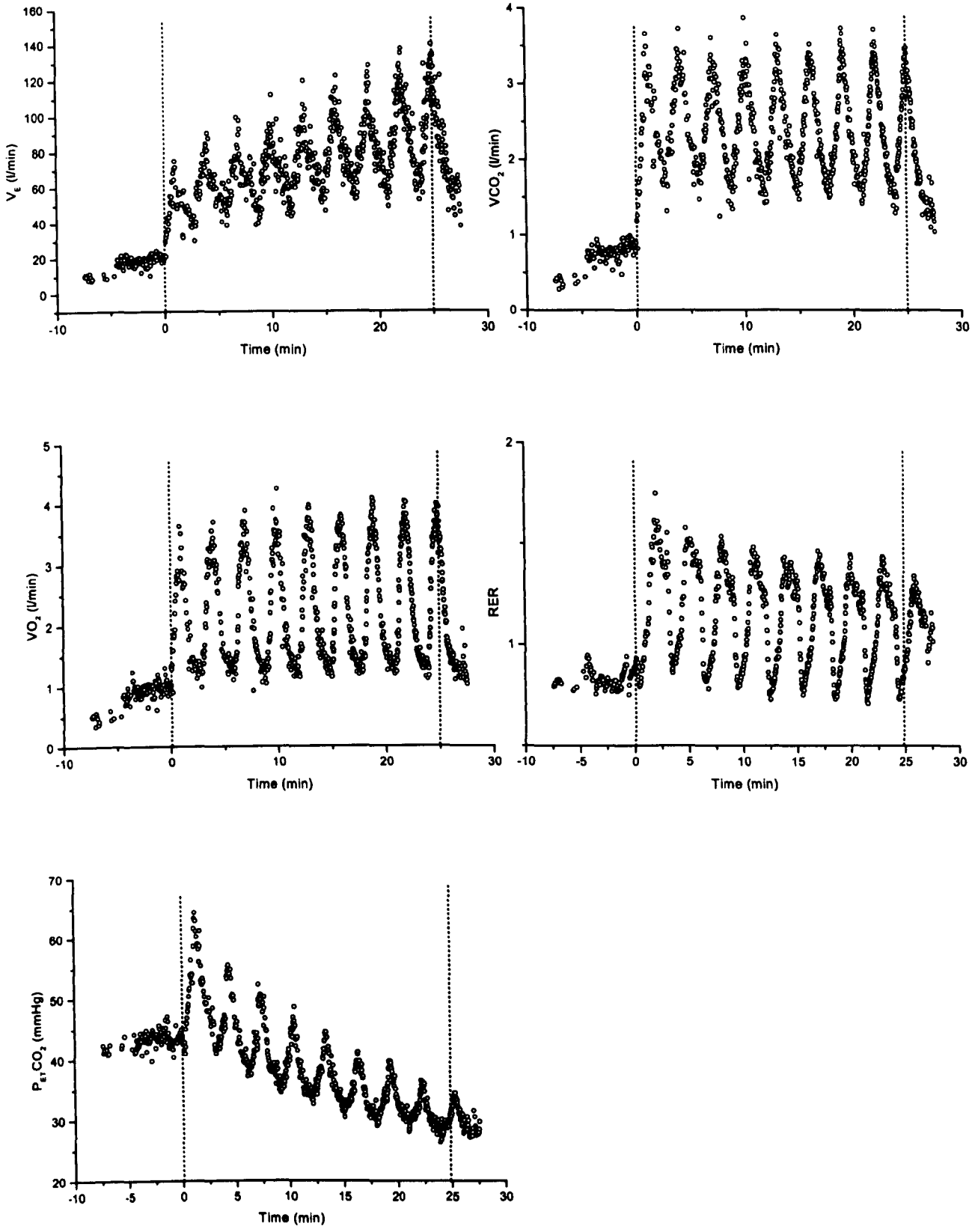
Appendix 3.6: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 2 during a 60s:120s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



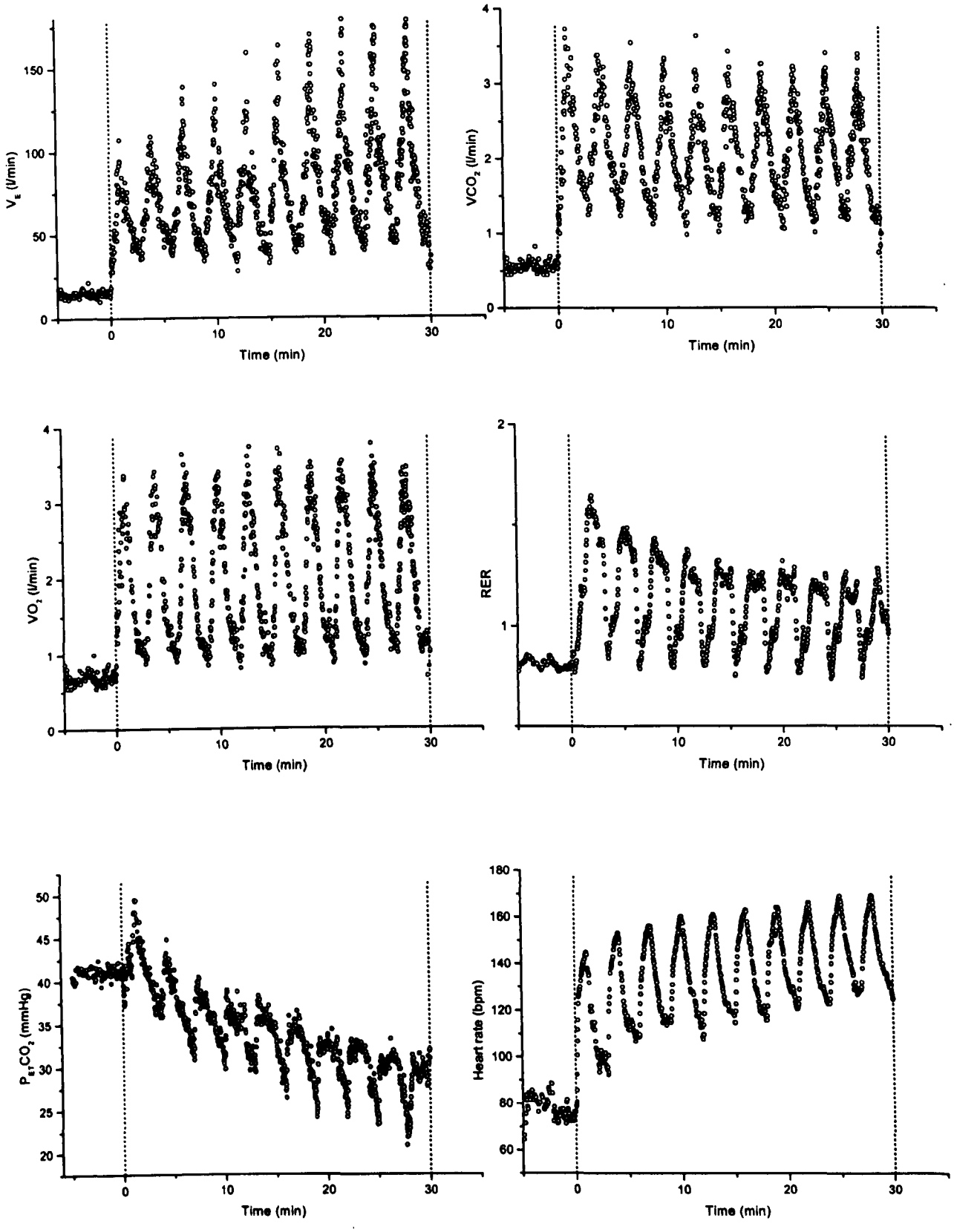
Appendix 3.7: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 3 during a 60s:120s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



Appendix 3.8: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 4 during a 60s:120s intermittent exercise test. The vertical dashed lines indicate the beginning and the premature end of the thirty-minute period of intermittent exercise.

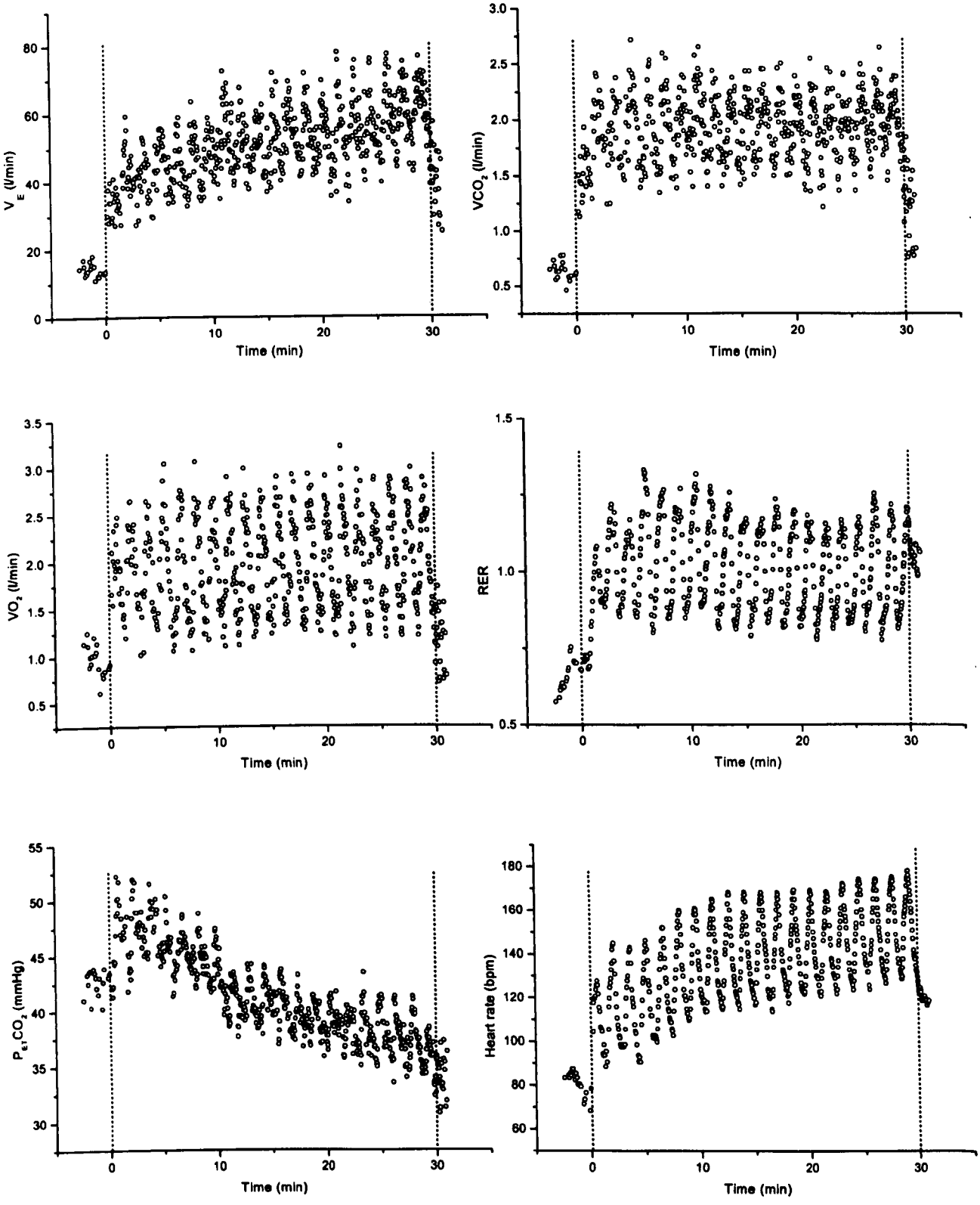


Appendix 3.9: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 5 during a 60s:120s intermittent exercise test. The vertical dashed lines indicate the beginning and the premature end of the thirty-minute period of intermittent exercise.

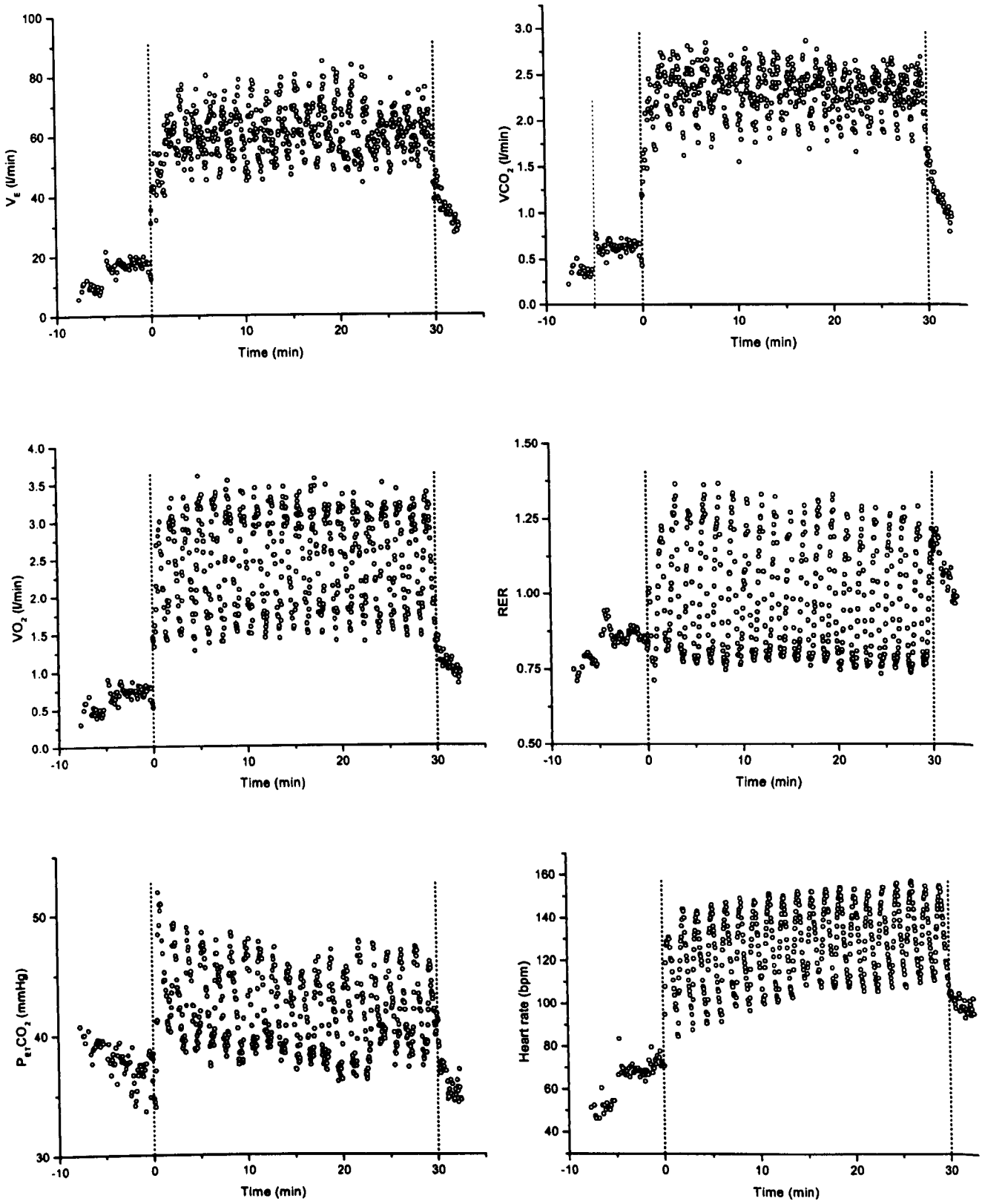


Appendix 3.10: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 6 durin a 60s:120s intermittent exercise test. The vertical dashed lines indicate the beginning and the end of the thirty-minute period of intermittent exercise.

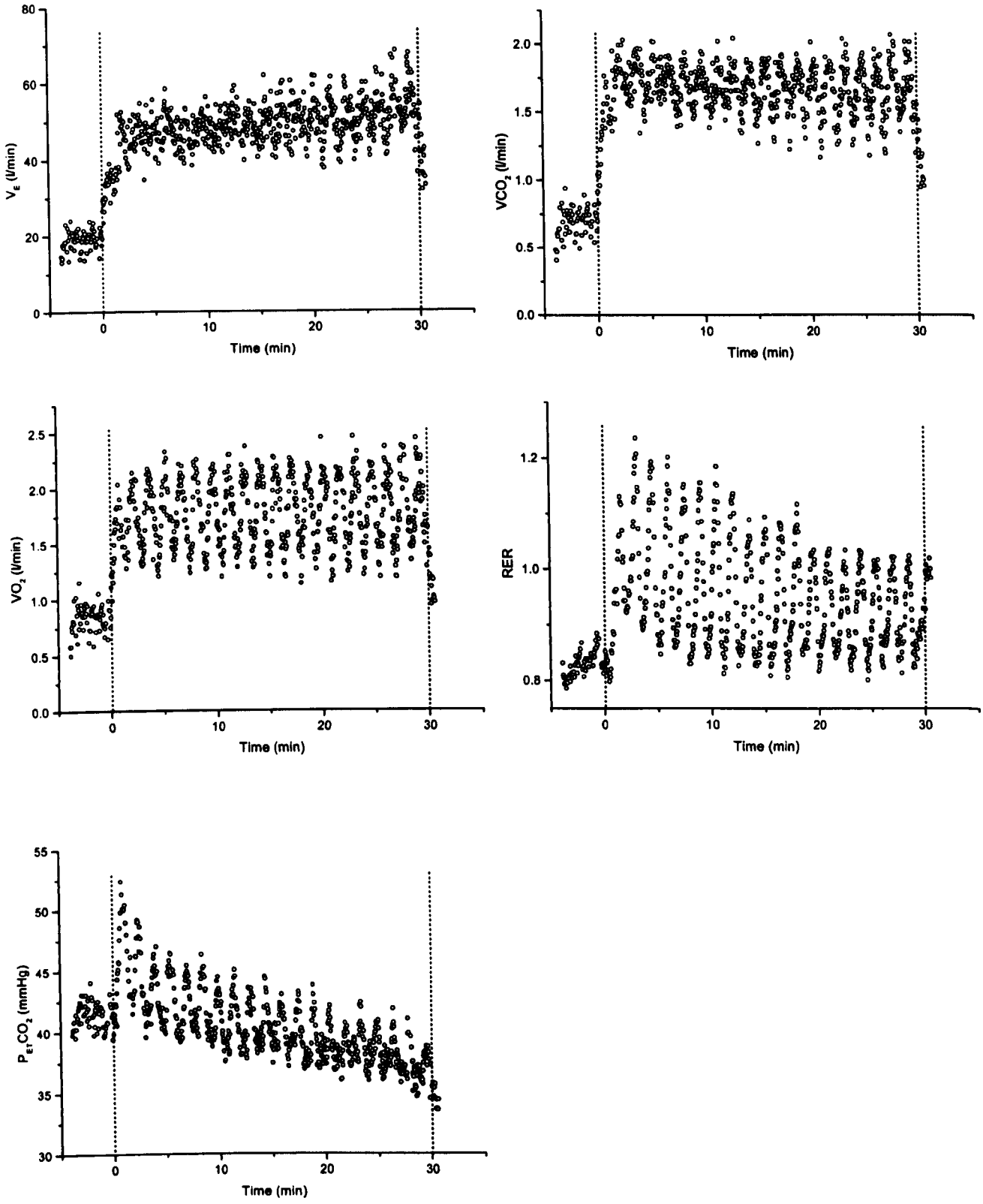
Appendix 3.4



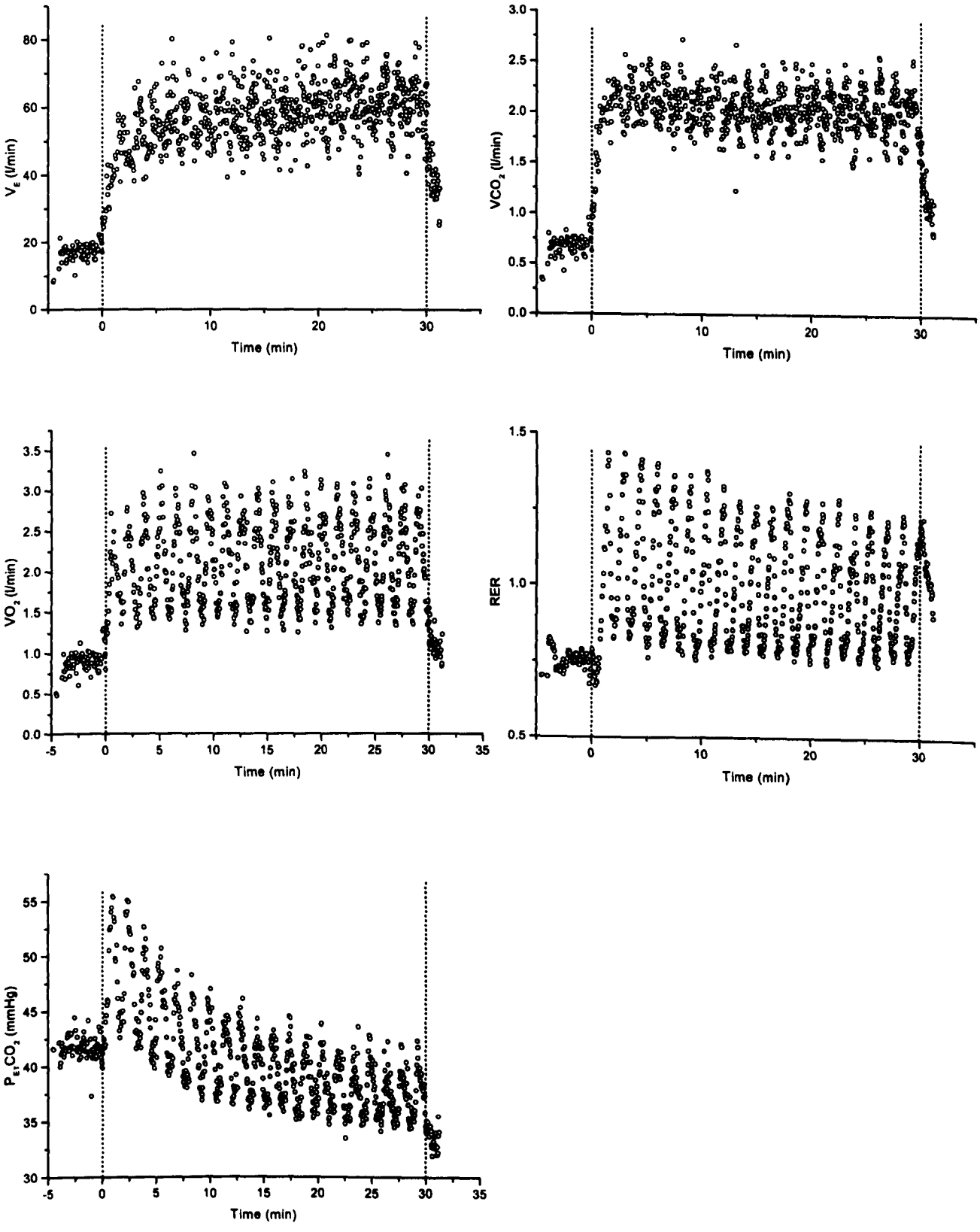
Appendix 3.11: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 2 during a 30s:60s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



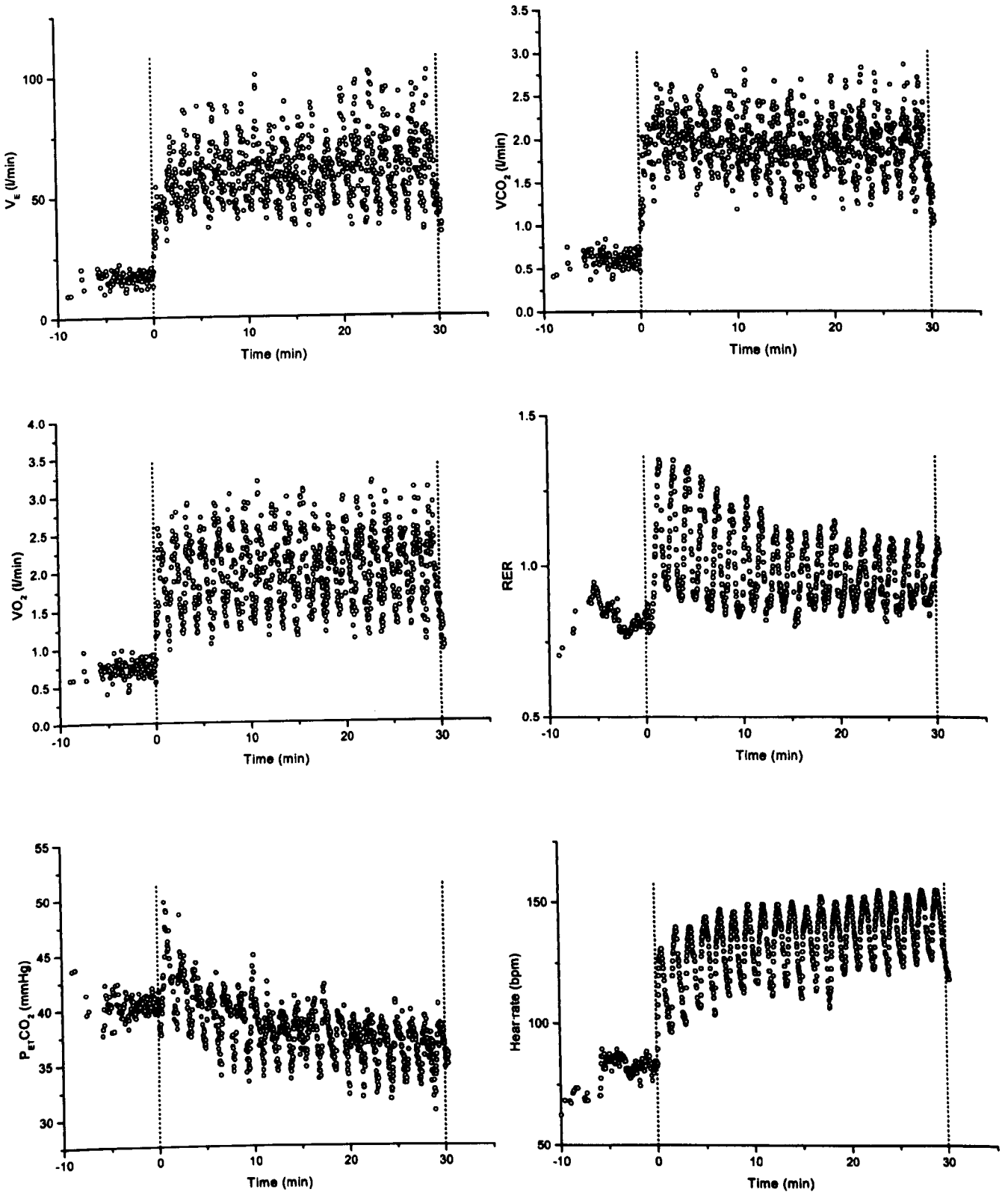
Appendix 3.12: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 3 during a 30s:60s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



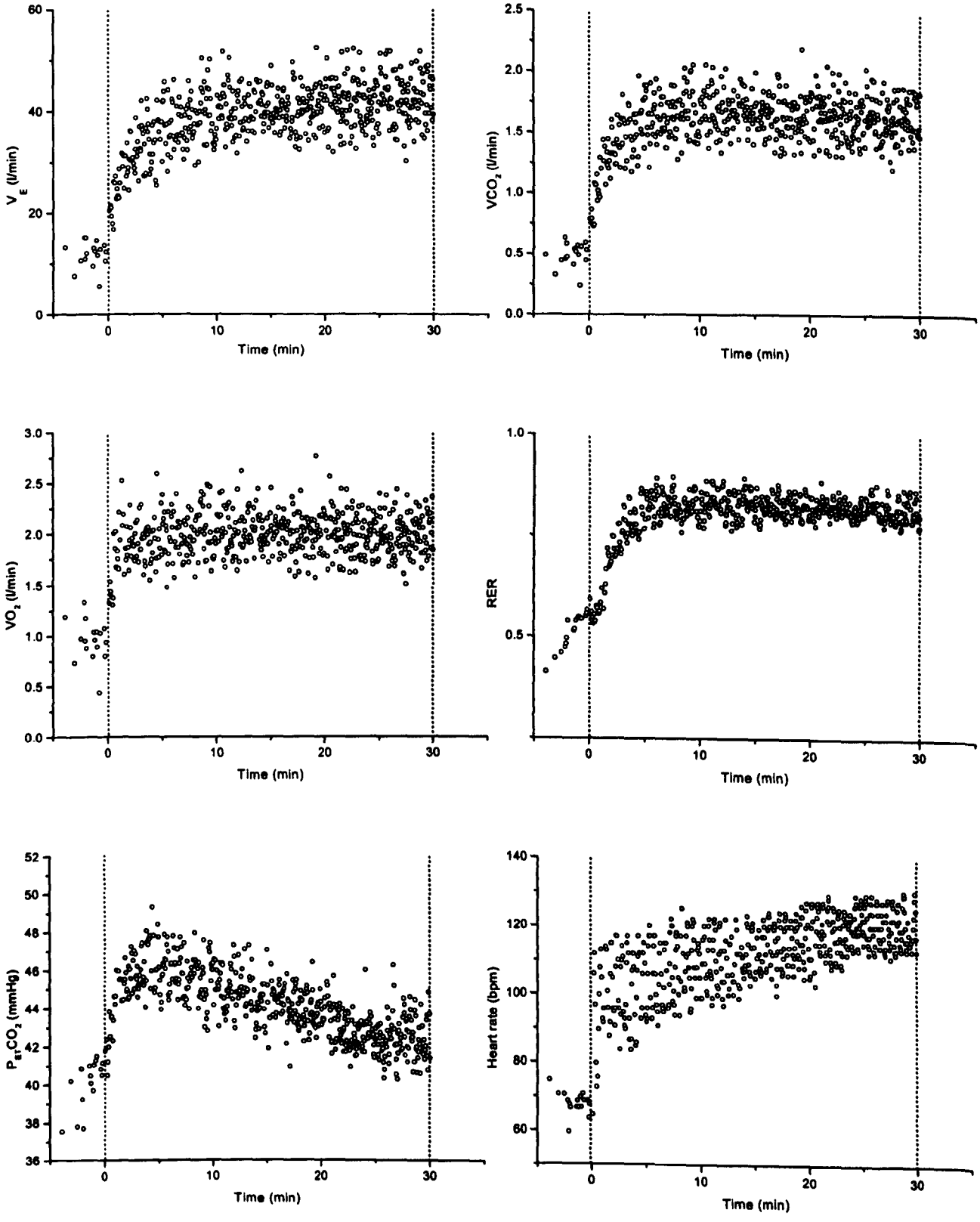
Appendix 3.13: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 4 during a 30s:60s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



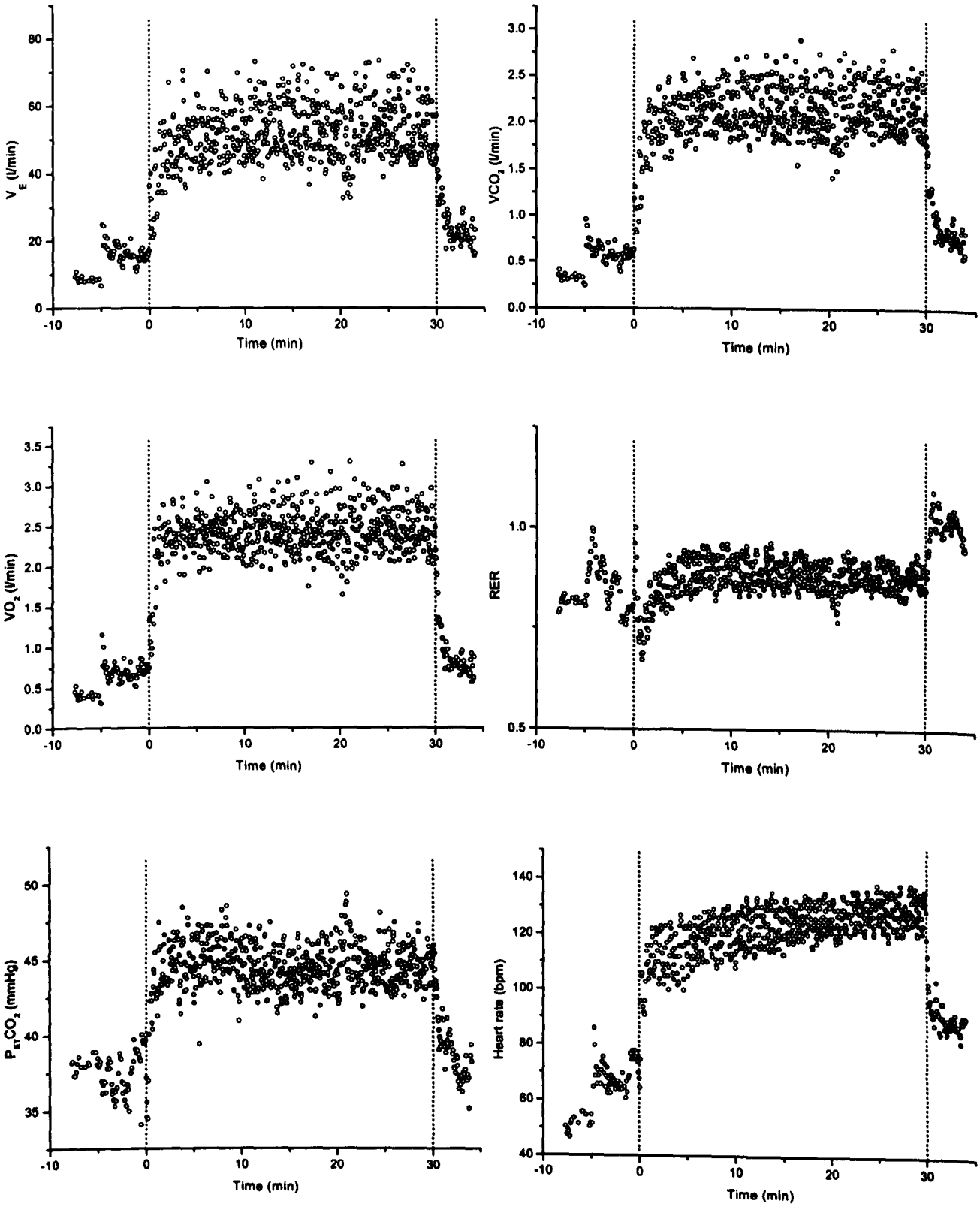
Appendix 3.14: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 5 during a 30s:60s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



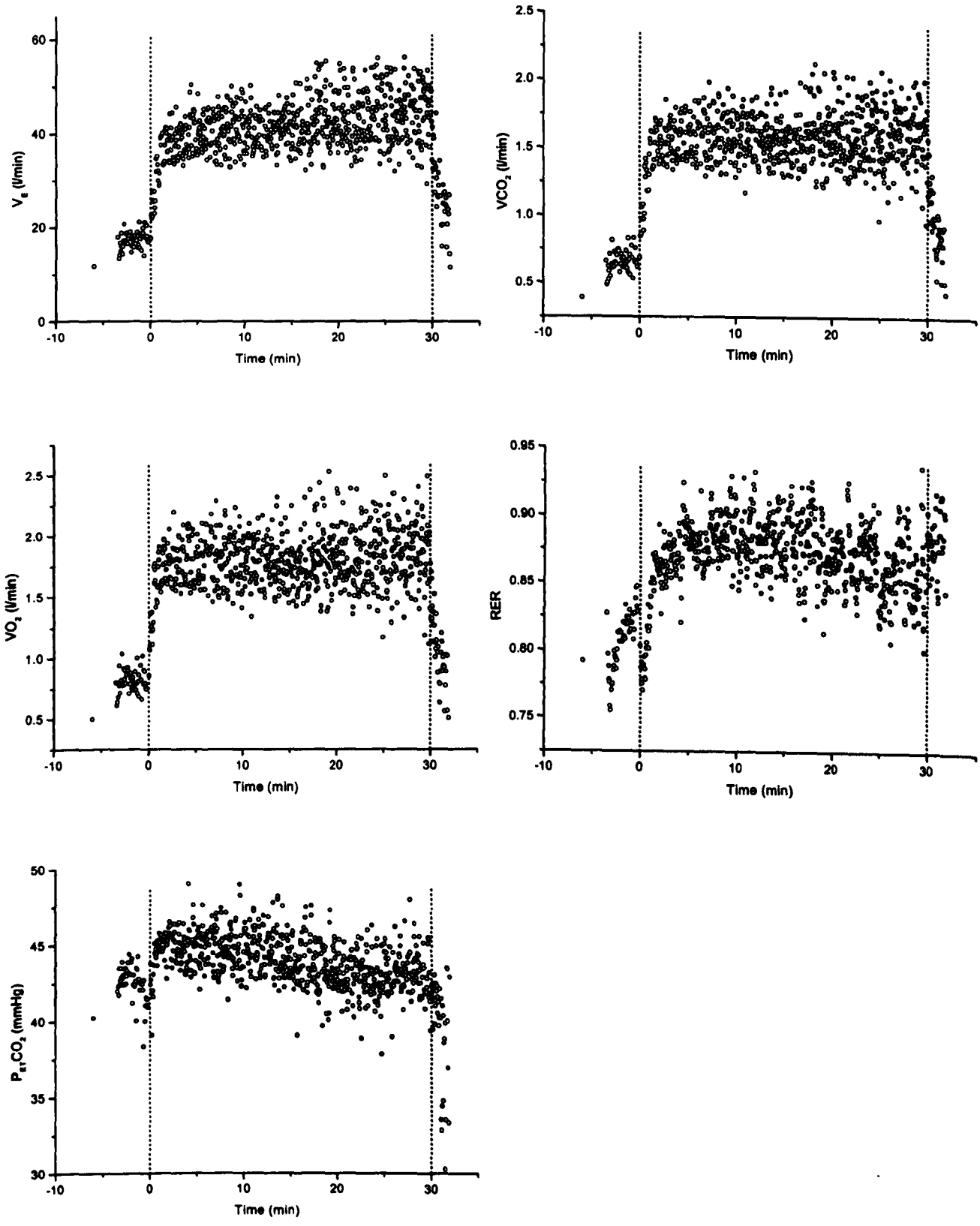
Appendix 3.15: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 6 during a 30s:60s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



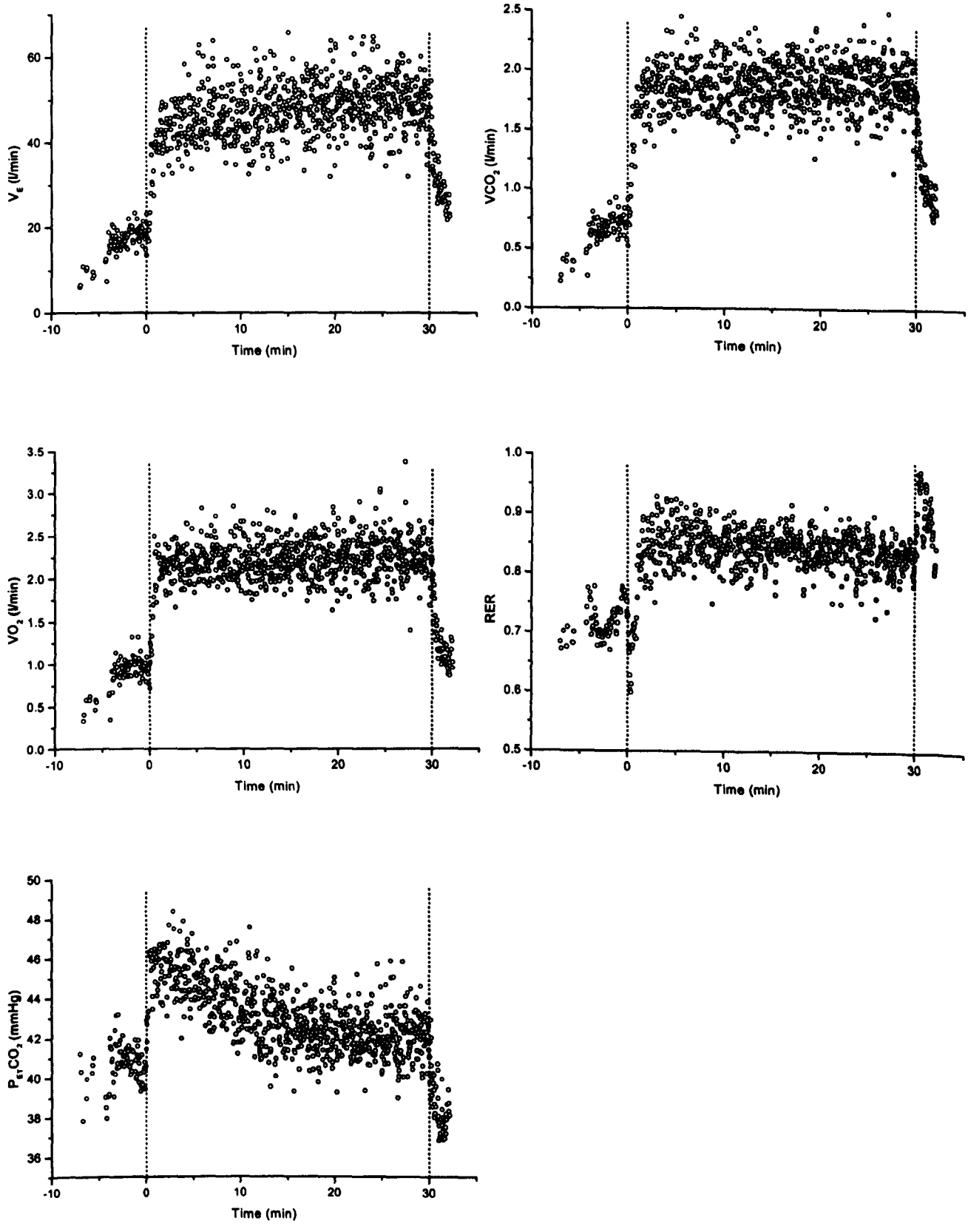
Appendix 3.16: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 2 during a 10s:20s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



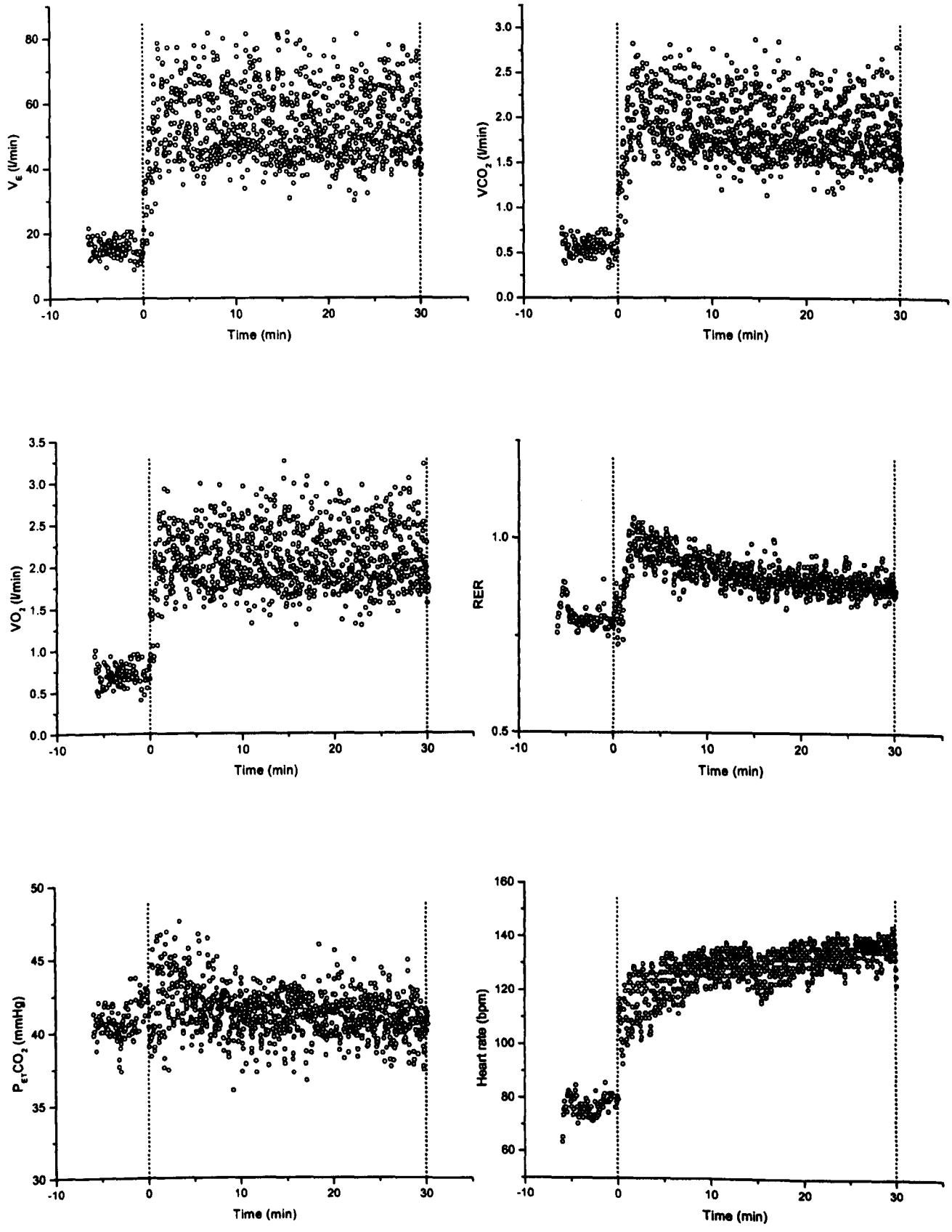
Appendix 3.17: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 3 during a 10s:20s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



Appendix 3.18: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 4 during a 10s:20s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



Appendix 3.19: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 5 during a 10s:20s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.



Appendix 3.20: Breath-by-breath ventilatory, pulmonary gas exchange and heart rate responses of subject 6 during a 10s:20s intermittent exercise test. The vertical dashed lines indicate the beginning and end of the thirty-minute period of intermittent exercise.

Appendix 4.1

University of Glasgow
Institute of Biomedical and Life Sciences
University of Glasgow

INFORMATION SHEET

TITLE OF INVESTIGATION: Effects of increased "dead space" on the ventilatory response to exercise in healthy humans

We invite you to participate in an investigation which we believe to be of potential importance. In order to help you to understand what the investigation is about, we are providing you with the following information. Be sure you understand it before you formally agree to participate. Ask any questions you have about the information which follows. We will do our best to explain and to provide any further information you require. You have been selected as a possible participant in this investigation because you are in good health.

The mechanisms that determine the ability to sustain moderate to severe exercise are poorly understood. Such information, however, is crucial if we are to improve exercise tolerance (i.e. the ability of individuals to perform exercise) in both health (e.g. elite athletes) and disease (e.g. patients with lung or heart disease). This study aims to study how breathing is controlled during exercise.

Testing will take place in the Laboratory of Human Physiology, West Medical Building at Glasgow University. You will be asked to visit the laboratory on up to sixteen occasions and to take part in the following tests:

Progressive Exercise Test: You will be asked to perform a maximal progressive exercise test on a stationary computer-controlled cycle so that we can noninvasively assess your level of fitness (i.e. by your maximal oxygen uptake and the work rate where you first start to produce lactic acid – the "lactate threshold"). During this test, the load will increase over the course of 15-25 minutes until you have to stop cycling either because of fatigue or breathlessness. You will repeat this test on up to three further occasions. On at least one occasion, you will perform the test while breathing through a wide-bore tube (approx. 30-50 cm long , and 5 cm diameter) – this resembles a snorkel tube. This intervention will cause your breathing to increase slightly, and we wish to examine the size of this response and how quickly it develops.

Submaximal test - constant load test: On separate days, you will cycle at moderate and high exercise intensities (below and above the lactate threshold) for periods ranging between 5 - 20 minutes, preceded and followed by 5-0 minutes of unloaded cycling. The total test duration will be no more than one hour.

Arterial blood oxygen saturation will be monitored continuously noninvasively from a finger or an ear lobe by pulse oximetry. Intramuscular oxygen saturation will be monitored continuously and noninvasively from the surface of the right or left quadriceps muscle using near infra-red spectroscopy.

Breathlessness and Rating of Perceived Exertion will be monitored at intervals throughout tests, using either a standard Borg scale (i.e. numbers with word anchors to help you rate a variable) or

a visual analogue scale (VAS) (the VAS scale consists of a horizontal line: the word "none" is placed at one end of the scale and the word "very severe" at the other). You will be asked provide a response which relates to your level of Breathlessness and Rating of Perceived Exertion using these scales.

During the exercise tests, you may breathe through a rubber mouthpiece which is similar to that used for snorkeling, and wear a noseclip. You may experience difficulty swallowing while breathing through a mouthpiece and wearing a noseclip, due to some pressure in the ears. Some subjects experience increased salivation when breathing through a mouthpiece. Some subjects experience mild discomfort from prolonged sitting on the seat of the cycle ergometer.

Exercise has a negligible risk in healthy adults, although maximal exercise has a small risk of inducing myocardial ischaemia. The primary symptom of myocardial ischaemia is chest pain on exertion. If you experience any unusual sensations in your chest during the experiment, you should cease exercising immediately. Your heart rate will be monitored via adhesive surface electrodes for the monitoring of the heart's electrical activity (the "electrocardiogram").

Before you become a subject, you will complete a medical questionnaire. People who have asthma, heart related and/or circulatory problems, hypertension or any other contraindicated condition will not be allowed to take part in the study.

All information obtained both from the preliminary medical questionnaire and from the study itself will be treated confidentially. It is our intention to publish the results of this study, but not in a way which will not enable individuals or their performance to be identified.

You are free to leave the study at any time. The outcome of the study may not benefit you directly. Some parts of the study constitute a possible transient risk to your health. There is a small cardiac risk to your health. You may feel uncomfortable during certain stages of the tests.

If you are worried about any unwanted side effects from any of the above procedures, you should contact:

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Consent Form

I,.....(PRINT)

of.....

give my consent to the research procedures which are outlined above, the aim, procedures and possible consequences of which have been outlined to me

by.....

Signature.....Date.....

Appendix 5.1

University of Glasgow
Institute of Biomedical and Life Sciences
University of Glasgow

INFORMATION SHEET

Plasticity of ventilatory control to exercise in healthy subjects

We invite you to participate in an investigation which we believe to be of potential importance. In order to help you to understand what the investigation is about, we are providing you with the following information. Be sure you understand it before you formally agree to participate. Ask any questions you have about the information which follows. We will do our best to explain and to provide any further information you require. Some terms will require us to provide you with further, verbal explanation; these have been highlighted in the text.

'What is the purpose of the study?': The mechanisms that determine the ability to sustain moderate to severe exercise are poorly understood. Such information, however, is crucial if we are to improve the ability of individuals to perform sustained physical activity habitually, in both healthy individuals and patients with lung or heart disease. This study therefore aims to study how breathing is controlled during exercise.

'Why am I being asked to participate in the study?': You are being asked to participate because you are in good health. Before you become a subject, you will be asked to complete a medical questionnaire. People who have asthma, heart-related and/or circulatory problems, hypertension or any other contraindicated condition will not be allowed to take part in the study. Women who are pregnant will be excluded.

'Where will the testing take place?': Testing will take place in the Laboratory of Human Physiology, West Medical Building at Glasgow University.

'How long will the study last?': You will be asked to visit the laboratory on typically eight, but no more than sixteen occasions. Each visit will last no longer than an hour and a half. If possible, we would prefer you to attend at the same time of day for each visit, i.e. the morning or the afternoon. At least three days will be allowed between consecutive visits.

'What will I be asked to do?': We would like you to first perform a ***progressive maximal exercise test*** on a stationary computer-controlled cycle. During this test, the load will increase over the course of 15-25 minutes, as if you were riding the cycle up a hill that becomes progressively steeper, until you feel that you have to stop. At this point, it most usual for subjects to feel leg tiredness and/or to feel short-of-breath. The results of this test will allow us to assess your level of fitness, in terms of (a) the work rate where your muscles first start to produce a substance called ***lactic acid*** and you start to feel tired and (b) the highest rate at which you can take oxygen into your lungs during the exercise.

Subsequently and on separate days, we would like you to complete a series of ***submaximal exercise tests***, again on the cycle. During these tests, you will be asked to cycle at a fixed work rate for periods ranging between 5 and 20 minutes, at an intensity ranging from ***moderate*** to ***heavy***.

Prior to each exercise test, we will ask to you perform some simple stretching exercises (under supervision) to help your muscles warm-up and then to complete about 5 minutes of ***freewheeling*** on the cycle. At the end of each test, the freewheeling will be repeated, and then the stretching.

'What measurements will be made'?: During the tests, we will make several non-invasive measurements.

(a) The level of your breathing and the composition of your breath will be measured continuously with a ***flow sensor*** which is placed close to your mouth, and a ***mass spectrometer*** which samples a small amount of the air that you breathe in and out. This will require you to breathe through a rubber mouthpiece which is similar to that used for snorkelling, and to wear a noseclip.

(b) The electrical activity of your heart and the rate at which your heart is beating will be measured continuously and noninvasively with an ***electrocardiogram***, from self-adhesive pads placed on the skin at several points on your chest.

(c) The level of oxygen in your blood will be measured continuously and noninvasively with an ***oximeter*** that slips over one of your fingers.

(d) At intervals during the tests, you will be asked to indicate the degrees to which you perceive being short-of-breath and having tiredness in your legs, using a simple ***rating scale***.

"What discomforts might I experience?': The level of discomfort is typically negligible. However, some subjects may experience slight discomfort.

(a) While breathing through the mouthpiece-noseclip system, a little short-lasting discomfort may be experienced when swallowing, because of a small and transient pressure build-up in the ears.

(b) Increased salivation may be experienced when breathing through a mouthpiece.

(c) Mild discomfort from prolonged sitting on the seat of the cycle may be experienced.

'Are there any risks in my taking part in the study?': The risks associated with the study are negligible. Exercise has a negligible risk in healthy adults, although maximal exercise has a small risk of inducing ***myocardial ischaemia***. The primary symptom of myocardial ischaemia is chest pain on exertion. If you experience any unusual sensations in your chest during the experiment, you should cease exercising immediately.

All information obtained both from the preliminary medical questionnaire and from the study itself will be treated confidentially. It is our intention to publish the results of this study, but not in a way which will not enable individuals or their performance to be identified.

You are free to leave the study at any time. The outcome of the study may not benefit you directly.

If you are worried about any unwanted side effects from any of the above procedures, you should contact:

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Centre for Exercise Science and Medicine, West Medical Building, Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow, G12 8QQ

Consent Form

I,.....(PRINT)

of.....

give my consent to the research procedures which are outlined above, the aim, procedures and possible consequences of which have been outlined to me

by.....

Signature.....Date.....