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**Yoshiga, C, Dawson, EA, Volianitis, S, Warberg, J and Secher, NH (2019) Cardiac output during exercise related to plasma atrial natriuretic peptide but not to central venous pressure in humans. *Experimental Physiology*. ISSN 1469-445X**

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Cardiac output during exercise related to plasma atrial natriuretic peptide but not to central venous pressure in humans

C. Yoshiga <sup>1</sup>, E.A. Dawson <sup>1,2</sup>, S. Volianitis <sup>1,3</sup>, J. Warberg <sup>4</sup>, N.H. Secher <sup>1</sup>

<sup>1</sup> Department of Anaesthesia, The Copenhagen Muscle Research Centre, Rigshospitalet, University of Copenhagen, Denmark, <sup>2</sup> Faculty of Science, School of Sport and Exercise Sciences, Liverpool John Moores University, United Kingdom, <sup>3</sup> Department of Health Science and Technology, Aalborg University, Denmark, <sup>4</sup> Department of Biomedicine, The Panum Institute, University of Copenhagen, Denmark

**Running title:** Cardiac output during exercise

**Key words:** atrial natriuretic peptide, cardiac output, central venous pressure, rowing

**Number of words:** 3970

**Number of references:** 26

**Corresponding author:**

Stefanos Volianitis, Ph.D., D.Sc.

Department of Health Science and Technology

Aalborg University

Fredrik Bajers Vej 7 E4

DK-9220 Aalborg

Denmark

Email: [svolian@hst.aau.dk](mailto:svolian@hst.aau.dk)

**Subject Area:** Human/environmental and exercise physiology

## **New Findings**

- What is the central question of this study?

Is cardiac output during exercise dependent on central venous pressure?

- What is the main finding and its importance?

The increase in cardiac output during both rowing and running is related to preload to the heart as indicated by plasma atrial natriuretic peptide but unrelated to central venous pressure. The results indicate that in upright humans central venous pressure reflects the gravitational influence on central venous blood rather than preload to the heart.

## **Abstract**

**Aim:** This study evaluated the increase in cardiac output (CO) during exercise in relation to central venous pressure (CVP) and plasma arterial natriuretic peptide (ANP) as expressions of preload to the heart. **Methods:** Seven healthy subjects (four men;  $26 \pm 3$  years;  $181 \pm 8$  cm height; and  $76 \pm 11$  kg, weight; mean  $\pm$  SD) rested in sitting and standing positions (in randomized order) and then rowed and ran at submaximal workloads. The CVP was recorded, CO (Modelflow) calculated, and arterial plasma ANP determined by radioimmunoassay. **Results:** While sitting CO was  $6.2 \pm 1.6$  l/min, plasma ANP  $70 \pm 10$  pg/ml, and CVP  $1.8 \pm 1.1$  mmHg (mean  $\pm$  SD) and decreased to  $5.9 \pm 1.0$  l/min,  $63 \pm 10$  pg/ml, and  $-3.8 \pm 1.2$  mmHg, respectively when standing ( $P < 0.05$ ). Ergometer rowing elicited an increase in CO to  $22.5 \pm 5.5$  l/min as plasma ANP increased to  $156 \pm 11$  pg/ml and CVP to  $3.8 \pm 0.9$  mmHg ( $P < 0.05$ ). Similarly, CO increased to  $23.5 \pm 6.0$  l/min during running with albeit smaller ( $P < 0.05$ ) increase in plasma ANP, but with little change in CVP ( $-0.9 \pm 0.4$  mmHg). **Conclusion:** The increase in CO in response to exercise is related to preload to the heart as indicated by plasma ANP, but unrelated to CVP. The results indicate that in upright humans CVP reflects the gravitational influence on central venous blood rather than preload to the heart.

## **Introduction**

When humans stand up gravity pools blood to dependent regions of the body (Matzen *et al.*, 1991). Thus, the “indifference point” (where pressure does not change during head-up or -down tilt) for venous pressure is at the level of the diaphragm (Gauer and Thron, 1965), while for volume (Perko *et al.*, 1997; Jarvis and Pawelczyk, 2010) and diameter of the inferior caval vein the indifference point is below the liver (Petersen *et al.*, 2014). Consequently, in an upright posture, central venous pressure (CVP) becomes negative, in parallel with reduction in the central blood volume and, therefore, preload to the heart and cardiac output (CO) decreases (Matzen *et al.*, 1991; Harms *et al.*, 2003). The central blood volume is often taken as the blood within the thoracic cavity as monitored by electrical impedance by Perko *et al.* (1997) and Jarvis and Pawelczyk (2010). Yet, it is the diastolic filling of the heart that is important for the ability to increase CO but diastolic filling of the heart cannot be determined during whole body exercise as rowing. However, it is straightforward to determine plasma atrial natriuretic peptide (ANP) that is released by distension of the atria and not related to CVP. Furthermore, plasma ANP decreases when central blood volume is reduced in response to head-up tilt (Matzen *et al.*, 1990), whole body heating (Vogelsang *et al.*, 2012) and pressure breathing (Schütten *et al.*, 1987), while CVP is reduced in the first two conditions and elevated in the latter. This disparity in CVP and ANP responses to central blood volume changes suggests that CVP may be less sensitive compared to plasma ANP in tracking central blood volume changes. Thus, the influence of CVP on preload to the heart during whole body exercise can be evaluated in relation to concomitant changes in plasma ANP.

During exercise leg muscles pump blood towards the heart (Beecher *et al.*, 1936; Rowell, 1993) as illustrated by enhanced plasma ANP (Vogelsang *et al.*, 2006). We hypothesized that even though orthostasis reduces CVP, nevertheless, the enhanced cardiac preload, as reflected by plasma

ANP, supports the increase in CO. A comparison was made between running and rowing because the seated position of rowing was considered to be associated with only a small gravitational reduction in CVP, thereby allowing for evaluation of CVP on the increase in CO during exercise.

## **Materials and Methods**

*Ethical Approval.* Seven healthy subjects (4 males, mean  $\pm$  SD,  $26 \pm 3$  years,  $181 \pm 8$  cm, and  $76 \pm 11$  kg) following informed oral and written consent, volunteered to the study as approved by the Ethical Committee of Copenhagen (KF 01-186/2) conforming to the Declaration of Helsinki, except for registration in a database. All subjects were recruited from a local club and, as part of their training were familiarized with ergometer rowing over several years.

*Experimental design and procedures.* After instrumentation, the subjects rested supine for about 15 min and then performed, in random order, rowing on an ergometer (Concept II, Morrisville, VT, USA) and walking followed by running on a treadmill (Runrace, Technogym, Gambettola, Italy). The two types of exercise were at three intensities aiming at heart rate (HR) of 120, 140, and 160 beats per minute and lasted about 7 min each.

*Oxygen uptake and pulmonary ventilation.* Pulmonary ventilation ( $V_E$ ) and oxygen uptake ( $VO_2$ ) were determined by an Oxyscreen metabolic cart (CPX/D; Medical Graphics, St. Paul, MN, USA) with values reported as the average over 15-s for the last minute of observation.

*Cardiovascular variables.* The CVP was measured with a catheter advanced to the right atrium following cannulation of an arm vein and values averaged over several heartbeats. Mean arterial pressure (MAP) was determined from the radial artery of the non-dominant arm. Both catheters were connected to transducers (Baxter Healthcare Corporation, Irvine, CA, USA) positioned on the back at the level of the papilla with infusion of isotonic saline ( $3 \text{ ml h}^{-1}$ ) to avoid clot formation.

A modified Modelflow method estimated CO from the radial arterial pressure (Finapres Medical Systems, Amsterdam, the Netherlands) to yield stroke volume that multiplied by HR estimates CO (Wesselling *et al.*, 1983) and values were adjusted to CO values calculated by the Fick principle. HR was recorded from a three-lead electrocardiogram with electrodes (Medicotest Q-10-A, Copenhagen, Denmark) placed on the sternum and the cervical vertebrae to minimize noise from muscles. All data were collected in the last minute of exercise and, similarly, in the last minute of rest.

#### *Blood samples*

Blood was sampled from the radial artery and the central venous catheter in tubes prepared with heparin and analyzed for pH, oxygen saturation (SO<sub>2</sub>) and tension (PO<sub>2</sub>) (ABL, Radiometer, Copenhagen, Denmark). Also, arterial samples (in EDTA tubes) were centrifuged and plasma kept at -80 °C until analyzed for ANP by radioimmunoassay (Schütten *et al.*, 1987). The ANP analysis has a sensitivity of 3.1 pg/ml and an intra- and inter-assay coefficient of variation were 4% and 5%, respectively.

*Statistical Analysis.* Data are presented as mean ± SD and comparisons across exercise mode and intensity evaluated by two-way ANOVA with Newman-Keuls post-hoc validation. Relations were evaluated separately for each type of exercise by linear and logarithmic regressions and a  $P < 0.05$  was considered statistically significant.

## **Results**

From sitting to standing position HR increased, while MAP, CO, VO<sub>2</sub>, and V<sub>E</sub> did not change significantly (Table 1). On the other hand, CVP, plasma ANP, and venous SO<sub>2</sub> decreased according to the postural change ( $P < 0.05$ ).

#### *Running*

From standing rest to running, HR, CO,  $\text{VO}_2$  and  $\text{V}_E$  increased, while MAP was maintained, CVP remained negative and plasma ANP increased (Table 1;  $P < 0.05$ ). Venous  $\text{PO}_2$  and  $\text{SO}_2$  decreased with exercise intensity ( $P < 0.05$ ) with no significant change in blood pH. The increase in CO was curvilinear related to the plasma ANP ( $r^2 = 0.94$ ,  $P < 0.05$ ), while the correlation to CVP if anything was negative and similar correlations were established when  $\text{VO}_2$  and blood gas variables were applied to calculate CO: for plasma ANP ( $r^2 = 0.94$ ,  $P < 0.05$ ); for CVP ( $r^2 = 0.54$ ,  $P < 0.05$ ) (Fig. 1).

### *Rowing*

Similar to running, HR, CO,  $\text{VO}_2$  and  $\text{V}_E$  increased with rowing intensity but the increases were more pronounced (Table 1). MAP did not increase significantly, but in contrast to running, both CVP and plasma ANP increased, while venous  $\text{PO}_2$  and  $\text{SO}_2$  decreased with exercise intensity ( $P < 0.05$ ) and there was a small decrease in blood pH. Also, similar to running, CO was related to plasma ANP during rowing ( $r^2 = 0.95$ ,  $P < 0.05$ ) and in that situation, also to CVP ( $r^2 = 0.89$ ,  $P < 0.05$ ) as confirmed when CO was calculated based on Fick's principle: for plasma ANP ( $r^2 = 0.95$ ,  $P < 0.05$ ) and for CVP ( $r^2 = 0.88$ ,  $P < 0.05$ ) (Fig. 1). Taking the observations during rowing and running together, there was no correlation between CO and CVP ( $r^2 = 0.17$ ), while CO was correlated to plasma ANP ( $r^2 = 0.94$ ,  $P < 0.05$ ).

## **Discussion**

Accepting the gravitational influence on CVP and considering that imaging of the heart during whole body exercise is challenging, this study used plasma ANP to indicate filling of the heart. We found that exercise enhances cardiac preload, as evaluated by plasma ANP, in accordance with results by Nicolai and Zuntz (1914) who carried out such evaluation during treadmill walking using x-ray, and confirming the findings by (Vogelsang *et al.*, 2006).



In the standing posture CVP decreased to -3.8 mmHg corresponding to a column of blood in the inferior caval vein of some 5 cm reflecting the distance to the pressure indifference point likely positioned at the level of the diaphragm (Gauer and Thron, 1965). In the abdominal cavity venous pressure could be influenced by the abdominal muscles pressing on the organs and the caval vein. Thus, in the open “central” veins the influence of gravity on pressure does not extend all the way to the “first” venous valve at end of the femoral vein. Conversely, CVP did not become negative during sitting on the ergometer likely because the subjects were in a position that would press the legs against the abdomen and thereby apply pressure to the caval vein. Similarly, we consider it likely that during rowing the pressure applied by the legs against the abdomen would contribute to the increase in CVP (Pott *et al.*, 1997). Also, during rowing the stroke is accomplished by stabilizing the trunk by a “Valsalva-like maneuver”, and thus, fluctuations in blood pressure are more related to the rhythm of rowing than to the function of the heart (Clifford *et al.*, 1994). Even though, in the present study, CVP data were not synchronized with each rowing stroke we can speculate that CVP fluctuated markedly within one rowing cycle and reached maximal value during the stroke as influenced by the entrained respiration (Mahler *et al.* 1991, Steinacker *et al.* 1993, Pott *et al.* 1997). In contrast, CVP demonstrated a small further decrease during running from the value established during standing and we can only speculate that this decrease was a manifestation of low abdominal pressure on the inferior caval vein but we lack data on intra-abdominal venous pressure during running and rowing.

The increase in preload to the heart, as indicated by plasma ANP and increased CO during exercise manifested despite the CVP decreased during running and increased during rowing indicating that CVP does not dictate filling of the heart. The relationship between CO and plasma ANP illustrates the importance of the Starling “law of the heart” for cardiovascular control, but it should be considered that during exercise there is sympathetic influence on the heart, as illustrated by an attenuated CO

response to exercise following beta-adrenergic blockade (Pawelczyk *et al.*, 1992). Taken together, CVP is not what drives blood into the ventricles, but filling of the ventricles depends on the amount of blood in the atria and close-by veins that is advanced to the ventricles by “suction” during the diastole as the heart is “untwisting” (Nakatani, 2011; <https://www.youtube.com/watch?v=N6ORMHi9rcU>). Consequently, CVP cannot be used for monitoring the central blood volume, except in heart failure patients whose hearts have lost the ability to “twist”.

The data indicate that a larger preload is needed for a given CO during rowing than during running although MAP did not increase (and HR was matched) and therefore, on average, afterload to the heart was the same during the two exercise interventions. Unfortunately, SV was not recorded in alignment with the stroke of rowing, but we speculate that the Valsalva-like maneuver associated with rowing has hindered the increase in CO during approximately half of the stroke. Thus, CO during rowing is likely to depend on ventricular filling in the part of the stroke where the rower did not hold his breath.

As expected when the workload for rowing and running was matched to a given HR,  $\text{VO}_2$  (and  $V_E$ ) was larger during rowing than during running given the orthostatic increase in HR as the central blood volume decreases (e.g. Matzen *et al.*, 1991) as indicated by the reduction in plasma ANP, as well as the reduction in venous oxygenation. During running the maximal HR can be calculated as  $208 - 0.7 \times \text{age}$  of the subjects (Tanaka *et al.*, 2001), i.e. around 190 bpm for the present subjects, while for rowing the maximal HR is only little more than 180 bpm (e.g. Volianitis *et al.*, 2008), in accordance with a lower HR in supine than upright positions (Stenberg *et al.*, 1967). Accordingly, a HR of 160 bpm would correspond to approximately a 90% effort during rowing, but only a 84% effort during running, and that the relative workload was larger during rowing than during running is illustrated by that only during rowing blood pH decreased but a maximal effort and rating of perceived effort were not

included in the protocol.

Limitations to the study include that plasma ANP indicates filling of mainly the right atrium and not diastolic filling of the (left) ventricle, but in the present study it was not possible to make an, e.g. echocardiographic evaluation of (left) ventricular filling during the two modes of exercise. Also, we accept that determination of CO could have been made by more conventional methods, as by thermodilution following placement of a pulmonary artery catheter, or by following the concentration in blood of ICG or technetium which we have used in previous evaluations of CO during exercise (Pawelczyk *et al.* 1992; Secher *et al.* 1977). Also, the study did not address whether there is a sex difference in the plasma ANP response to exercise, although women are reported to demonstrate a level that is about twice as high as men (Clark *et al.* 1990).

In conclusion, the present results suggest that the “muscle pump” contributes significantly to enhance CO during exercise, as indicated by plasma ANP for evaluation of preload to the heart. On the other hand, in an upright posture CVP can both increase and decrease in response to exercise and the deviations are unrelated to the gradually increasing plasma ANP level with exercise intensity. We consider these findings to reflect on the evaluation of circulation during exercise. Quite often total peripheral resistance during exercise is expressed by subtracting CVP from MAP, even though the inclusion of a pump (i.e. muscle pump) while expressing a resistance seems unjustified from a physics perspective. The present findings suggest that in upright humans CVP is not a “resistance” to venous return but a reflection of the gravitational influence on venous blood and independent of how much blood is present in the veins, as long as they stay open, which is the definition of “central” veins.

### **Author contributions**

All authors contributed to conception and design of experiments, collection and assembly of data, data

analysis and interpretation and manuscript writing. All authors approved the final version of the Manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed. Research governance was by NHS.

### **Acknowledgments**

This study was supported by a Foundation for Comprehensive Research on Aging and Health from the Ministry of Health, Labour, and Welfare and a Grant-in-Aid for Scientific Research(C) from the Ministry of Education, Culture, Sports, Science, and Technology (no. 13680077). We thank Elsa Larsen for technical help in determination of plasma ANP.

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Table 1. Variables (mean  $\pm$  SD) at sitting and standing rest and during rowing and running at three levels of targeted heart rate (HR).

	Rest		HR 120		HR 140		HR 160	
	Sitting	Standing	Rowing	Running	Rowing	Running	Rowing	Running
HR, bpm	79 $\pm$ 8	90 $\pm$ 7	115 $\pm$ 13 ‡	117 $\pm$ 13	138 $\pm$ 17 ‡	139 $\pm$ 18 †	159 $\pm$ 15 ‡	158 $\pm$ 16 †
MAP, mmHg	92 $\pm$ 6	91 $\pm$ 5	97 $\pm$ 4	93 $\pm$ 4	97 $\pm$ 3	93 $\pm$ 3	96 $\pm$ 4	92 $\pm$ 4
CVP, mmHg	1.8 $\pm$ 1.1	-3.8 $\pm$ 1.2	2.7 $\pm$ 0.9 *	-5.4 $\pm$ 1.2	3.1 $\pm$ 1.1 *	-5.4 $\pm$ 0.9	3.8 $\pm$ 0.9 *	-4.7 $\pm$ 0.8
ANP, pg/ml	70 $\pm$ 10	63 $\pm$ 10	107 $\pm$ 9 ‡*	76 $\pm$ 10 †	135 $\pm$ 10 ‡*	97 $\pm$ 11 †	156 $\pm$ 11 ‡*	104 $\pm$ 11 †
CO, l/min	5.0 $\pm$ 1.3	5.2 $\pm$ 0.9	18.1 $\pm$ 6.4 ‡	16.4 $\pm$ 3.9 †	20.4 $\pm$ 6.4 ‡	22.6 $\pm$ 7.0 †	22.5 $\pm$ 5.5 ‡	23.5 $\pm$ 6.0 †
VO <sub>2</sub> , l/min	0.41 $\pm$ 0.1	0.47 $\pm$ 0.1	1.98 $\pm$ 0.7 *	1.65 $\pm$ 0.5 †	2.52 $\pm$ 0.8 *	2.36 $\pm$ 0.8 †	2.98 $\pm$ 0.8 *	2.80 $\pm$ 0.7 †
VE, l/min	11.6 $\pm$ 3.2	12.4 $\pm$ 5.6	36.9 $\pm$ 10.0 *	33.8 $\pm$ 10.1 †	53.7 $\pm$ 10.8 *	49.2 $\pm$ 10.2 †	68.9 $\pm$ 9.8 *	62.1 $\pm$ 10.2 †
Hb, g/100ml								
Arterial	13.9 $\pm$ 1.5	13.8 $\pm$ 1.6	14.1 $\pm$ 1.4	13.8 $\pm$ 1.7	14.4 $\pm$ 1.6	14.1 $\pm$ 1.4	14.7 $\pm$ 2.7	14.0 $\pm$ 1.7
Venous	13.3 $\pm$ 2.7	13.0 $\pm$ 3.8	13.8 $\pm$ 1.7	13.1 $\pm$ 1.9	14.3 $\pm$ 2.7	13.3 $\pm$ 1.1	14.4 $\pm$ 2.7	13.3 $\pm$ 23.4
pH								
Arterial	7.42 $\pm$ 0.04	7.44 $\pm$ 0.02	7.41 $\pm$ 0.03	7.42 $\pm$ 0.01	7.40 $\pm$ 0.03	7.42 $\pm$ 0.02	7.40 $\pm$ 0.03	7.40 $\pm$ 0.04
Venous	7.39 $\pm$ 0.01	7.40 $\pm$ 0.01	7.38 $\pm$ 0.10	7.38 $\pm$ 0.01	7.36 $\pm$ 0.01	7.38 $\pm$ 0.01	7.32 $\pm$ 0.05 ‡*	7.38 $\pm$ 0.03
PO <sub>2</sub> , mmHg								
Arterial	106 $\pm$ 10	102 $\pm$ 11	94 $\pm$ 9	97 $\pm$ 3	93 $\pm$ 10	94 $\pm$ 7	90 $\pm$ 10 ‡	93 $\pm$ 9
Venous	36 $\pm$ 6	32 $\pm$ 3	27 $\pm$ 7	30 $\pm$ 6	24 $\pm$ 1 ‡	30 $\pm$ 6	23 $\pm$ 2 ‡	26 $\pm$ 3 †
SO <sub>2</sub> , %								
Arterial	98.9 $\pm$ 0.6	98.7 $\pm$ 1.0	98.0 $\pm$ 1.1	98.5 $\pm$ 0.2	97.6 $\pm$ 1.5	98.1 $\pm$ 0.7	97.3 $\pm$ 1.8	97.9 $\pm$ 1.0
Venous	60.1 $\pm$ 13.3	56.4 $\pm$ 6.1	44.1 $\pm$ 13.6	49.7 $\pm$ 13.6	37.3 $\pm$ 8.8 ‡	48.6 $\pm$ 11.3	34.3 $\pm$ 8.3 ‡	39.6 $\pm$ 3.5 †



MAP, mean arterial pressure; CVP, central venous pressure; ANP, atrial natriuretic peptide;  $VO_2$ , oxygen uptake; VE, pulmonary ventilation; Hb, blood haemoglobin;  $PO_2$ , partial pressure of oxygen;  $SO_2$ , haemoglobin oxygen saturation. \* Different from running; ‡ different from sitting rest; † different from standing ( $P < 0.05$ ).

## Legends

Figure 1. Logarithmic regressions between cardiac output (CO) and plasma atrial natriuretic peptide (ANP) (upper part) and linear regressions between CO and central venous pressure (CVP) (lower part) at rest and during three exercise intensities for running and rowing ( $n = 7$ ,  $P < 0.05$ ).

