Dynamic arterial elastance during experimental endotoxic septic shock

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Research

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Abstract

Background: Dynamic arterial elastance (Ea dyn), the ratio between pulse pressure variation (PPV) and stroke volume variation (SVV), has been suggested as a functional parameter that is a surrogate of arterial load. We aimed to determine the effects of endotoxic septic shock and hemodynamic resuscitation on Ea dyn .

Results: Experimental randomized study in a university animal research laboratory with 18 New Zealand rabbits. Animals received placebo (SHAM, n=6) or intravenous lipopolysaccharide (LPS, Escherichia coli serotype 055:B5, 1 mg·kg -1) with or without (EDX-R, n=6; EDX-NR, n=6) hemodynamic resuscitation (fluid bolus of 20 ml·kg -1 and norepinephrine for restoring mean arterial pressure). Continuous arterial pressure and aortic blood flow measurements were obtained simultaneously. Cardiovascular efficiency was evaluated by the oscillatory power fraction (%Osc: oscillatory work / left ventricular (LV) total work) and the energy efficiency ratio (EER = LV total work/cardiac output). The LPS-induced endotoxic shock produced a hyperdynamic shock with high cardiac output and arterial hypotension. Ea dyn increased in septic animals (from 0.73 to 1.70; p=0.012) and dropped after hemodynamic resuscitation. Ea dyn was related with the %Osc and EER [estimates: -0.101 (-0.137 – -0.064) and -9.494 (-11.964 – -7.024); p<0.001, respectively]. So, the higher the Ea dyn, the better the cardiovascular efficiency (lower %Osc and EER).

Conclusions: In this experimental model, Ea dyn increased during endotoxic septic shock and decreased with hemodynamic resuscitation. Sepsis resulted in a reduced oscillatory power fraction and lowered EER, reflecting a better cardiovascular efficiency that was tracked by Ea dyn . Ea dyn could be a potential index of cardiovascular efficiency during septic shock.

Background

Variations in left ventricular (LV) stroke volume (SV) and arterial pulse pressure (PP) are closely related to changes in intrathoracic pressure during respiration [1]. The magnitude of these changes has been used to define preload-dependency [2]. Since the change in arterial PP for a change in SV has the dimension of elastance, the ratio between the PP variation (PPV) and SV variation (SVV) has been described as dynamic arterial elastance (Ea_{dyn}). This parameter has been proposed as a functional measure of the arterial load [3]. It arises from the simultaneous assessment of PP and SV changes during a respiratory cycle and is related to the cardiac modulation of volume as a function of pressure [3]. Although Ea_{dyn} was initially defined as a variable describing central arterial tone, we have shown in an experimental rabbit model that Ea_{dyn} is affected not only by arterial factors but also by the heart rate (HR) and the pattern of blood flow during experimental changes in arterial load conditions [4]. Moreover, we have recently demonstrated a significant relationship between Ea_{dyn}, ventriculo-arterial coupling, and LV mechanical efficiency[5]. Accordingly, Ea_{dyn} could be considered as a composite index reflecting the interaction between both arterial and cardiac factors and potentially providing valuable information regarding cardiovascular performance and ventriculo-arterial coupling.

Although the primary function of the cardiovascular system is to deliver hydraulic energy (expressed in terms of blood flow and arterial pressure) to sustain normal physiological functions, there is an optimal combination of cardiac function and arterial system status that provides the maximum efficiency in transferring this mechanical energy from the LV to the arterial tree[6]. Prior studies have demonstrated that this ideal combination occurs when the ventricle and the arterial tree are optimally coupled [7, 8].

Septic shock has a profound impact on macrohemodynamics and also the microcirculation [9, 10]. Macrocirculatory derangements in septic shock have been characterized by a combination of a variable degree of cardiac dysfunction and a profound vasoplegia [11]. These alterations are usually the expression of a ventricular-arterial uncoupling associated with a sepsis-induced cardiovascular inefficiency [9, 12]. Moreover, septic shock has also been associated with early and sustained microcirculatory derangements that may evolve independently of macrohemodynamics[13].

Since Ea_{dyn} has been shown to be affected by both arterial and cardiac factors, we hypothesized that sepsis-induced hemodynamic cardiovascular dysfunction could affect Ea_{dyn}. We, therefore, aimed to determine the effects of endotoxic septic shock on Ea_{dyn}, and the impact of hemodynamic resuscitation.

Methods

Eighteen New-Zealand rabbits (weight 2.5 ± 0.1 kg), supplied by the Reproduction Laboratory of the University of Cadiz, were maintained at a controlled temperature (23°C) in individual cages on a 12-h light/dark cycle with free access to food and water up to the time of experimental procedures. Animals were allowed to acclimatize to the laboratory for one week before the beginning of the experiments. All methods and protocols in this investigation were reviewed and approved (project 06-04-15-230) by the Ethical Committee for Animal Experimentation of the School of Medicine of the University of Cadiz (license 07–9604) and the Dirección General de la Producción Agrícola y Ganadera of the Junta de Andalucía. Animal care and use procedures conformed to national and European Union regulations and guidelines (Spanish Royal Decree 53/2013 and EU Directive 2010/63/EU).

Anesthesia and instrumentation. Animals were premedicated with an intramuscular dose of xylazine (10 $mg \cdot kg^{-1}$) and ketamine (40 $mg \cdot kg^{-1}$). Then they were tracheotomized and their lungs mechanically ventilated in volume-controlled mode (Servo 900c, Siemens-Elema, Solna, Sweden), with 8 $ml \cdot kg^{-1}$ of tidal volume, positive end-expiratory pressure of 0 cmH_2O, an inspiration to expiration ratio of 1:2, inspired oxygen fraction of 0.6, and a respiratory rate of 35-40 $breaths \cdot min^{-1}$ adjusted to maintain an end-tidal CO_2 between 35–45 mmHg. The right internal jugular vein was catheterized for continuous sedation with ketamine (10–40 $mg \cdot kg^{-1} \cdot h^{-1}$) and midazolam (1–3 $mg \cdot kg^{-1} \cdot h^{-1}$). The muscular blockade was maintained with a rocuronium bromide infusion (0.6–1.2 $mg \cdot kg^{-1} \cdot h^{-1}$)[14]. Adequacy of anesthesia before neuromuscular blockade and through the experiment was evaluated by the absence of any significant blood pressure and/or heart rate change in response to an external noxious stimulus. A Ringers lactate solution (6 $ml \cdot kg^{-1} \cdot h^{-1}$) was administered as a maintenance fluid therapy. Temperature was continuously

monitored by a rectal probe and maintained between 38–40º using a heating pad. A 22G sterile polyethylene catheter was introduced into the right femoral artery and connected to a pressure transducer (TruWave, Edwards Lifesciences LLC, Irvine, CA, USA). This was zeroed against atmospheric pressure, and optimal damping of the arterial waveform was checked by a square wave test. The left femoral vein was used to administer vasoactive drugs and fluid bolus.

Hemodynamic monitoring. A pediatric esophageal Doppler probe (KDP72; CardioQ Combi, Deltex Medical, Chichester, UK) was introduced into the esophagus until the best outline and maximal peak velocity of aortic blood waveform was obtained. Cardiac output (CO) was calculated using the minute distance of aortic blood flow, which represents the distance traveled by a column of blood in 1 min and is calculated by the Doppler system as the product of HR and the velocity-time integral of the aortic flow waveform. The arterial pressure signal was transferred from the multi-parametric monitor (S/5, Datex-Ohmeda, Helsinki, Finland) to the Doppler system and automatically synchronized with the aortic blood flow waveform for pressure-flow analysis.

Evaluation of arterial load. A 3-element Windkessel model was used for characterizing the arterial system[15], consisting of systemic vascular resistance [SVR=mean arterial pressure (MAP) / CO]; arterial compliance (C_{art}= stroke volume / arterial pulse pressure)[16] and characteristic impedance (Zc). Zc represents the arterial input impedance in the absence of arterial wave reflections[17]. Assuming that arterial reflections are negligible during early systole[17, 18], Zc was estimated as the slope of the early ejection pressure-flow relationship, using the ratio between the maximum of the first derivate of pressure and flow averaged during one minute [19, 20].

The effective arterial elastance (Ea) was used as a lumped parameter of arterial load accounting for both mean and pulsatile components[21]:

[Please see the supplementary files section to view the equation.]

Where R_T is the total mean vascular resistance (SVR + Zc), t_s and t_d are systolic and diastolic periods, respectively, and τ the diastolic time constant ($\tau = SVR \times C_{art}$) [21].

PPV, SVV, and dynamic arterial elastance. PPV was calculated as the percentage changes in arterial pulse pressure during a ventilatory cycle as [(PPmax – PPmin) / (PPmax + PPmin) /2] × 100, where PPmax and PPmin represent the maximal and minimal arterial pulse pressure, respectively. The calculation of SVV was performed similarly. SVmax and SVmin were calculated by integrating the systolic component of aortic blood flow waveform, whereas PPV was derived from the femoral arterial pressure waveform. PPV and SVV values were simultaneously analyzed and averaged during 1-min using a custom Excel macro (Microsoft Corporation, Redmond, WA, USA) (Figure 1). Ea_{dyn} was calculated as PPV/SVV [22].

Left ventricular energetics. Left ventricular energetics were analyzed from the instantaneous pressure and flow recordings. Aortic blood flow and femoral arterial pressure waveforms were recorded simultaneously during at least 20 seconds at 180 Hz and ensemble-averaged, foot-to-foot aligned using the maximum of

the second derivative, and interpolated to the duration of the cardiac cycle to provide a representative waveform for analysis. An illustrative example of the signal processing is shown in Figure 2. The contribution of kinetic energy was considered negligible and not included in the analysis[18].

The left ventricular (LV) total power ($\dot{W}_{tot}$) transferred to the systemic circulation was calculated as the time-averaged integral of the instantaneous product of blood pressure (P) by flow (Q) during the whole cardiac period (T):

[Please see the supplementary files section to view the equation.]

The product of mean pressure by mean flow, or steady power ($\dot{W}_{std}$), corresponds to the energy maintaining forward blood flow and represents the fraction of $\dot{W}_{tot}$ useful for organ perfusion [18, 23, 24].

[Please see the supplementary files section to view the equation.]

The oscillatory power ($\dot{W}_{osc}$) refers to the energy lost in pulsatile phenomena due to cardiac contractions:

[Please see the supplementary files section to view the equation.]

Cardiovascular efficiency. The oscillatory power fraction (%Osc) represents the portion of $\dot{W}_{tot}$ wasted in oscillatory power and quantifies the efficiency with which the external mechanical power was transferred into useful work from the LV to the arterial system [23-25]. Therefore, the lower the %Osc, the more efficiently LV external work is delivered to the arterial system and converted into useful work for creating blood flow. %Osc has been used as a measure of the optimization of ventriculo-arterial coupling[23, 24].

[Please see the supplementary files section to view the equation.]

We also calculated the LV power necessary for generating one unit cardiac output for a given arterial load, as the energy efficiency ratio (EER) [25, 26]:

[Please see the supplementary files section to view the equation.]

Therefore, the lower the EER, the lower the energy required for generating blood flow for a given LV afterload.

Tissue O_2 saturation. Tissue oxygen saturation (StO_2) was used as a surrogate for microcirculatory perfusion. StO_2 was continuously assessed by using near-infrared spectroscopy (NIRS) with the INVOS 5100C monitor (Covidien, Boulder, CO, USA), as previously described[27]. A neonatal self-adhesive sensor was placed over a shaved and cleaned skin of the lateral area of the hind leg (*biceps femoris* muscle), contralateral to the femoral venous access. The sensor was held on place with adhesive tape and covered with an opaque wrapper to avoid ambient light interference. Measurements were obtained every 4 secs, and 1-min averaged for analysis.

We also considered the ratio between LV mechanical work and StO_2 as a measure of the work required for the cardiovascular system for given tissue perfusion, which represents an index of the performance of the coupling between the central hemodynamics and the microcirculation.

[Please see the supplementary files section to view the equation.]

So, the lower the Mmi, the lower the LV mechanical work required for sustaining tissue perfusion.

Experimental protocol. After completion of the surgical procedures, animals were allowed to stabilize MAP and HR (variation <5%) at least for 10 minutes. After that, they were assigned using a computer-generated random sequence to three groups (6 animals each): a sham-operated group (SHAM), a septic group (EDX), and a septic group with hemodynamic resuscitation (EDX-R). In septic animals, a purified lipopolysaccharide (LPS) prepared from Escherichia coli serotype 055:B5 (Sigma Chemical, St. Louis, MO) was intravenously infused over 10 mins through the femoral vein (1 $mg \cdot kg^{-1}$ diluted in normal saline for a total volume of 8 ml, and flushed by 2 ml of normal saline to ensure a complete delivery). The dose and rate of LPS administration were previously established on a pilot experiment with 8 animals, in which the dose was varied from 1 to 2 $mg \cdot kg^{-1}$. SHAM animals received an equivalent amount of normal saline. Three hours after LPS infusion, animals in the EDX-R group received a fluid bolus of 20 $ml \cdot kg^{-1}$ for 10 min. A norepinephrine infusion started at 0.25 $mcg \cdot kg^{-1} \cdot min^{-1}$ was started after fluid administration if MAP was below the baseline level. Norepinephrine was increased by 0.10 $mcg \cdot kg^{-1} \cdot min^{-1}$ every 3 mins until reaching a MAP value similar to the baseline level (±5% deviation). Hemodynamic measurements, aortic blood flow, and arterial pressure waveforms were recorded a least during 1 min at baseline and every hour up to 4 hours after LPS or placebo administration. In EDX-R animals, measurements after fluid bolus (post-infusion) and norepinephrine infusion (which corresponds to 4 hours after LPS infusion) were also obtained. After completion of the study protocol, animals were euthanized using a lethal dose of intravenous potassium chloride under deep anesthesia. Animal death was confirmed by verification of the absence of blood flow and arterial pressure tracings.

Statistical analysis. Data are expressed as the mean ± standard deviation or median (25^{th} to 75^{th} interquartile). The normality of data was checked by the Shapiro Wilk test. Differences between groups at baseline were performed using a one-way analysis of variance (ANOVA), and differences over time were assessed by two-way mixed ANOVA for repeated measurements. The Greenhouse–Geisser correction was used when the Mauchly test detected violation of sphericity. Whenever a significant interaction was found, pairwise comparison between groups was performed using a one-way ANOVA with the Tukey-Kramer test. Mixed-effect regression analyses were used to evaluate the impact of sepsis on the relationship between Ea_{dyn} (the dependent variable) and arterial load (Ea, and its determinants: SVR, C, and Zc), cardiac function variables (heart rate and maximal acceleration of aortic blood flow, as an index LV performance[28]); cardiac energetics ($\dot{W}_{tot}$ and its components: $\dot{W}_{std}$ and $\dot{W}_{osc}$) and variables of cardiovascular efficiency (%Osc and EER). The effects of sepsis on Ea_{dyn} were evaluated in the EDX group and on animals in the EDX-R group before the hemodynamic resuscitation. Models were

constructed using individual animals and experimental groups as subjects for random factors, and experimental stages as repeated measurements with a heterogeneous first-order autoregressive covariance structure. Model selection based on the corrected Akaike's Information Criteria, in which lower scores indicate superior fit [29]. Model parameters were estimated via the restricted maximum likelihood method, and the estimated fixed effect of each parameter quantified by using estimated value and standard error (SE). A P value < 0.05 was considered statistically significant. All statistical analyses were two-tailed and performed using MedCalc Statistical Software version 19.1 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

Results

Variations in left ventricular (LV) stroke volume (SV) and arterial pulse pressure (PP) are closely related to changes in intrathoracic pressure during respiration [1]. The magnitude of these changes has been used to define preload-dependency [2]. Since the change in arterial PP for a change in SV has the dimension of elastance, the ratio between the PP variation (PPV) and SV variation (SVV) has been described as dynamic arterial elastance (Ea_{dyn}). This parameter has been proposed as a functional measure of the arterial load [3]. It arises from the simultaneous assessment of PP and SV changes during a respiratory cycle and is related to the cardiac modulation of volume as a function of pressure [3]. Although Ea_{dyn} was initially defined as a variable describing central arterial tone, we have shown in an experimental rabbit model that Ea_{dyn} is affected not only by arterial factors but also by the heart rate (HR) and the pattern of blood flow during experimental changes in arterial load conditions [4]. Moreover, we have recently demonstrated a significant relationship between Ea_{dyn}, ventriculo-arterial coupling, and LV mechanical efficiency[5]. Accordingly, Ea_{dyn} could be considered as a composite index reflecting the interaction between both arterial and cardiac factors and potentially providing valuable information regarding cardiovascular performance and ventriculo-arterial coupling.

Although the primary function of the cardiovascular system is to deliver hydraulic energy (expressed in terms of blood flow and arterial pressure) to sustain normal physiological functions, there is an optimal combination of cardiac function and arterial system status that provides the maximum efficiency in transferring this mechanical energy from the LV to the arterial tree[6]. Prior studies have demonstrated that this ideal combination occurs when the ventricle and the arterial tree are optimally coupled [7, 8].

Septic shock has a profound impact on macrohemodynamics and also the microcirculation [9, 10]. Macrocirculatory derangements in septic shock have been characterized by a combination of a variable degree of cardiac dysfunction and a profound vasoplegia [11]. These alterations are usually the expression of a ventricular-arterial uncoupling associated with a sepsis-induced cardiovascular inefficiency [9, 12]. Moreover, septic shock has also been associated with early and sustained microcirculatory derangements that may evolve independently of macrohemodynamics[13].

Since Ea_{dyn} has been shown to be affected by both arterial and cardiac factors, we hypothesized that sepsis-induced hemodynamic cardiovascular dysfunction could affect Ea_{dyn}. We, therefore, aimed to

determine the effects of endotoxic septic shock on Ea_{dyn}, and the impact of hemodynamic resuscitation.

Discussion

In this experimental animal study, Ea_{dyn} increased during endotoxic septic shock and decreased after fluid administration. The evolution of Ea_{dyn} was associated with both cardiac and arterial factors and cardiovascular efficiency. LPS infusion was associated with an early uncoupling between macro and microcirculation, expressed as the ratio between LV external mechanical work and tissue oxygen saturation. This condition was aggravated after hemodynamic resuscitation.

Relationship between Ea_{dyn} and cardiac and arterial variables

We found that heart rate and Zc, which represents the pulsatile component of the LV hydraulic workload related to arterial stiffness and aortic cross-sectional area[18], were the main variables associated to Ea_{dyn} in septic animals. Moreover, when considering only HR and Zc, 67% of the actual Ea_{dyn} values could be predicted in the septic animals. However, considering the magnitude of the relationship between Ea_{dyn} and Zc and HR, we cannot exclude that other determinants not contemplated in our simplified arterial and cardiac models may have contributed significantly to Ea_{dyn}.

These findings corroborate previous results about the compound nature of Ea_{dyn} and the impact of both cardiac and arterial factors. While net changes in Ea, a net measure of LV afterload, were negatively associated with Ea_{dyn}, variations in heart rate did so positively [4, 30]. Our results also confirm earlier observations about the impact of endotoxic septic shock on the PPV/SVV relationship. In a model of LPS-induced pneumonia in mechanically ventilated rats, Chenerpath *et al*. observed that the ratio PPV/SVV was higher in LPS-treated compared with untreated rats. Septic animals also showed a significant decrease in arterial tone, as reflected by an increase in net arterial compliance[31]. This study, together with our previous observations about the impact of changes in arterial load, support the notion that Ea_{dyn} does not represent a real measure of central arterial tone nor an index of the arterial stiffness, and that the concept of Ea_{dyn} as a variable describing LV afterload should be avoided[5].

Relationship between LV energetics and Ea_{dyn}

The force that pumps blood from the heart to the peripheral circulation is determined by an energy gradient that comprises a kinetic, gravitational, and a potential element[32]. During a contraction, the heart works increasing potential energy and, in a much smaller proportion, kinetic energy. This work is distributed to the systemic circulation generating the energy gradient that drives blood flow through to the systemic circulation and delivers adequate transport for oxygen and nutrients to the tissues. In turn, the hydraulic work generated by the ventricle can be divided into two components: steady and oscillatory work. While $\dot{W}_{std}$ represents the work per unit time that effectively contributes to blood flow and

peripheral perfusion, $\dot{W}_{osc}$ represents the unavoidable consequence of the pulsatile nature of the heart's activity and is considered "wasted" energy since it does not contribute to the net movement of blood to the peripheral circulation[18]. From this perspective, an efficient cardiovascular system would minimize the oscillatory component of LV mechanical work. The ratio $\dot{W}_{osc}/\dot{W}_{tot}$ (i.e., %Osc) becomes then a sort of index of the efficiency of the LV mechanical power dissipation in the arterial system[24]. Moreover, as the ability of the heart as a pump for generating power depends not only on the myocardial performance but also on the physical properties of the arterial system, %Osc represents also a measure of the efficiency of the matching between the heart and the arterial system [18, 24].

While in normal conditions $\dot{W}_{osc}$ accounts only about 10% of the total LV mechanical work[24, 33], which manifests the optimal efficiency of the arterial system for buffering cardiac pulsations, factors altering arterial load or heart rate are known to affect this balance[24, 34]. In our study, the overall %Osc at baseline was 11 ± 2%, similar to that reported in previous animal studies[24, 35]. While in SHAM animals %Osc remained unchanged, it significantly decreased during LPS infusion and increased after hemodynamic resuscitation. These modifications agree with the known relationship between Zc and HR and %Osc. Previous studies have shown that, when Zc decreases or heart rate increases, %Osc decreases [24, 34, 36, 37]. In our study, septic animals showed a progressive and significant decline in Zc and increased heart rate. Not surprisingly, these same factors were the main determinants of the Ea_{dyn} changes in septic animals. As Ea_{dyn} was directly related to $\dot{W}_{std}$ but inversely to $\dot{W}_{osc}$, Ea_{dyn} reflects then not only the net LV mechanical work but how this work is generated. Therefore, changes in Osc% and EER, which expresses the energy cost for each unit of cardiac output, were inversely associated with Ea_{dyn} variations. Accordingly, when cardiovascular efficiency increases, so does the Ea_{dyn} [5].

Our results differ from those reported by Cholley *et al*. in a similar study [35]. These authors found that a lower dose of LPS (600 $\mu g \cdot kg^{-1}$) resulted in a hypodynamic hemodynamic profile characterized by low cardiac output, arterial hypotension, and increased %Osc. Septic shock was also associated with a lower heart rate and higher Zc resulting from the aortic smooth muscle contraction and aortic wall edema. These discrepancies may likely reflect differences in the experimental setup, the dose of LPS, and the anesthetic regimen used (pentobarbital vs. ketamine + midazolam). However, even if our results differ in how LPS affects hemodynamics, both are coherent on the physiological mechanisms and how these factors are known to affect %Osc [24, 34, 36, 38].

Micro-macrocirculation coherence

In our study, the infusion of LPS produced a marked decrease in StO_2 and a mismatch between LV energetics and StO_2, which reflected the inability of the cardiovascular system to sustain tissue perfusion during the increased oxygen demands induced by sepsis. The overall LV mechanical power required for a given StO_2 during the whole experiment was 1.1 mW in SHAM animals, 1.4 mW in EDX animals, and mW in EDX-R 1.8 mW (3.1 mW after resuscitation). Therefore, even if cardiovascular efficiency improved in septic animals, this phenomenon did not lead to better tissue perfusion. Moreover, the LPS-related uncoupling between macrohemodynamics and microcirculation was aggravated after hemodynamic

resuscitation. These results emphasize the known dissociation between macro and microcirculation and the futility of normalizing systemic hemodynamics when the coherence between micro and macrocirculation has been lost [39, 40].

Limitations

Our assessment of the microcirculatory perfusion was based on the regional evaluation of muscular oxygenation, which may not represent the state of the global microcirculation. However, the muscular StO_2 has been demonstrated to offer a proper window for early detection of the microcirculatory derangements during sepsis due to its nonvital peripheral organ condition[27]. Furthermore, our septic shock model could be considered as a representation of an early septic shock, where macro and microcirculation should be still partially coupled. In the late stages of septic shock, the evolution and interaction of macro-hemodynamic and StO_2 could have been different[40].

Second, the evaluation of the cardiovascular efficiency was based on the analysis of the instantaneous arterial pressure-aortic blood flow relationship [18]. This analysis, however, does not represent the actual LV mechanical efficiency since it does not consider myocardial oxygen consumption [41]. Moreover, because of our simplified assessment of LV performance, we cannot determine the actual impact of LPS on myocardial performance, which would have required the invasive measurements of LV volume and pressure. However, we have recently demonstrated that Ea_{dyn} is significantly related to ventriculo-arterial coupling and LV efficiency using the data obtained from the LV pressure-volume analysis by the classical conductance catheter technique[42]. Our current results agree with the observations made in this study. Nevertheless, even if LPS infusion was associated with an improved transfer of the power from the LV to the arterial system, we cannot confirm that this condition was associated with a better myocardial contractility. As LPS can alter not only LV contractility but also loading conditions [43, 44], the decreased arterial load in septic animals may have played an essential role in the improved power transfer efficiency[24]: a low %Osc indicates therefore that, for a given LV myocardial performance, the arterial load was relatively lower. Thus, even if %Osc does not directly describe the ventricular-arterial coupling variables, it represents the efficiency of the system[23, 25].

Finally, our study was based on the evaluation assessment of the arterial pressure and blood flow using two independent methods for calculating PPV and SVV. The use of pulse-contour analysis for estimating SVV and Ea_{dyn} may lead to different results, as estimations based on this methodology may be exposed to the impact of arterial load[45] So, the usefulness of the pulse contour-derived Ea_{dyn} would eventually depend on how the pulse contour algorithm estimates SV changes over a respiratory cycle. If this estimation is reliable, Ea_{dyn} should be valid and reflect changes in cardiovascular efficiency.

Conclusions

During experimental endotoxic septic shock, Ea_{dyn} changes were associated with arterial and cardiac factors and significantly related to cardiovascular efficiency: the higher the efficiency of the

cardiovascular system on delivering the energy to the arterial system for sustaining blood flow, the higher the Ea_{dyn}. Therefore, Ea_{dyn} may be a valuable index for monitoring cardiovascular mechanical efficiency.

List Of Abbreviations

Ea_{dyn}: dynamic arterial elastance; PPV: pulse pressure variation; SVV: stroke volume variation; HR: heart rate; CO: cardiac output; SVR: systemic vascular resistance; MAP: mean arterial pressure; C: arterial compliance; Zc: characteristic impedance; Ea: effective arterial elastance; R_T: total mean vascular resistance; τ: diastolic time constant; LV: left ventricular; $\dot{W}_{tot}$: left total ventricular power; P: blood pressure; Q: aortic blood flow; T: cardiac period; $\dot{W}_{std}$: LV steady power; $\dot{W}_{osc}$: LV oscillatory power; %Osc: oscillatory power fraction; EER: energy efficiency ratio; StO_2: tissue oxygen saturation; NIRS: near-infrared spectroscopy; Mmi: macro-microcirculatory coupling index; SHAM: sham-operated group; EDX: endotoxic group without hemodynamic resuscitation; EDX-R: endotoxic group with hemodynamic resuscitation; LPS: lipopolysaccharide; ANOVA: analysis of variance; SE: standard error; CI: confidence interval.

Declarations

Ethics approval. All procedures and protocols in this study were reviewed and approved (project 06-04-15-230) by the Ethical Committee for Animal Experimentation of the School of Medicine of the University of Cadiz (license 07–9604) and the Dirección General de la Producción Agrícola y Ganadera of the Junta de Andalucía. Animal care and use procedures conformed to national and European Union regulations and guidelines (Spanish Royal Decree 53/2013 and EU Directive 2010/63/EU).

Consent for publication. Not applicable.

Availability of data and materials. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests. MIMG has received Honoraria and/or Travel Expenses from Edwards Lifesciences and Deltex Medical. AGC has received Honoraria and/or Travel Expenses from Edwards Lifesciences. A.R. has received Honoraria and is on the advisory board for LiDCO, Honoraria for Covidien, Edwards Lifesciences, and Cheetah. MC in the last 5 years received Honoraria and/or Travel Expenses from Edwards Lifesciences, LiDCO, Cheetah, Bmeye, Masimo, and Deltex. AM, PGG, MGR, and RMG have no conflict of interest to declare. The authors declare that they have no non-financial competing interests.

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Authors' contributions. MIMG conceived and designed the study, participated in the experiments, performed the statistical analysis, interpreted the data, and wrote the manuscript. PGG, PSO, MGR, AGC, and JM and participated in the experiments, interpreted the data, and helped to draft the manuscript. AM and AR have made substantial contributions to the analysis and interpretation of data, have been

involved in drafting the manuscript, and contributed to its critical review. MC contributed to the conception and design of the study, interpreted data, and wrote and reviewed the manuscript. All the authors read and approved the final version of the manuscript.

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References

1. Pinsky MR (1997) The hemodynamic consequences of mechanical ventilation: an evolving story. Intensive Care Med 23:493–503
2. Pinsky MR (2012) Heart lung interactions during mechanical ventilation. Curr Opin Crit Care 18:256–260
3. Monge Garcia M, Gracia Romero M, Gil Cano A, Aya HD, Rhodes A, Grounds R, Cecconi M (2014) Dynamic arterial elastance as a predictor of arterial pressure response to fluid administration: a validation study. Crit Care 18:626
4. Monge Garcia MI, Guijo Gonzalez P, Gracia Romero M, Gil Cano A, Rhodes A, Grounds RM, Cecconi M (2017) Effects of arterial load variations on dynamic arterial elastance: an experimental study. Br J Anaesth 118:938–946
5. Monge Garcia MI, Jian Z, Hatib F, Settels JJ, Cecconi M, Pinsky MR (2020) Dynamic Arterial Elastance as a Ventriculo-Arterial Coupling Index: An Experimental Animal Study. Frontiers in physiology 11:284
6. Guarracino F, Baldassarri R, Pinsky MR (2013) Ventriculo-arterial decoupling in acutely altered hemodynamic states. Crit Care 17:213
7. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K (1983) Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 245:H773–H780
8. Asanoi H, Sasayama S, Kameyama T (1989) Ventriculoarterial coupling in normal and failing heart in humans. Circ Res 65:483–493
9. Guarracino F, Ferro B, Morelli A, Bertini P, Baldassarri R, Pinsky MR (2014) Ventriculoarterial decoupling in human septic shock. Crit Care 18:R80
10. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166:98–104
11. Vieillard-Baron A, Cecconi M (2014) Understanding cardiac failure in sepsis. Intensive Care Med 40:1560–1563
12. Guarracino F, Bertini P, Pinsky MR (2019) Cardiovascular determinants of resuscitation from sepsis and septic shock. Crit Care 23:118

13. Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, Arnold RC, Colilla S, Zanotti S, Hollenberg SM, Microcirculatory Alterations in R, Shock I (2007) Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med 49: 88–98, 98 e81-82
14. Quesenberry KE, Carpenter JW (2012) Ferrets, rabbits, and rodents: clinical medicine and surgery. Elsevier/Saunders, St. Louis, Mo
15. Westerhof N, Lankhaar JW, Westerhof BE (2009) The arterial Windkessel. Med Biol Eng Comput 47:131–141
16. Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y (1998) Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol 274:H500–H505
17. Nichols WW, O'Rourke M (2005) McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical principles. Oxford University Press, London
18. Milnor WR (1989) Hemodynamics. Williams & Wilkins, Baltimore
19. Lucas CL, Wilcox BR, Ha B, Henry GW (1988) Comparison of time domain algorithms for estimating aortic characteristic impedance in humans. IEEE Trans Bio-med Eng 35:62–68
20. Li JK (1986) Time domain resolution of forward and reflected waves in the aorta. IEEE Trans Bio-med Eng 33:783–785
21. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, Kass DA (1992) Effective arterial elastance as index of arterial vascular load in humans. Circulation 86:513–521
22. Monge Garcia MI, Gil Cano A, Gracia Romero M (2011) Dynamic arterial elastance to predict arterial pressure response to volume loading in preload-dependent patients. Crit Care 15:R15
23. Cholley B, Le Gall A (2016) Ventriculo-arterial coupling: the comeback? J Thorac Dis 8:2287–2289
24. O'Rourke MF (1967) Steady and pulsatile energy losses in the systemic circulation under normal conditions and in simulated arterial disease. Cardiovascular research 1:313–326
25. Berger DS, Li JK, Noordergraaf A (1995) Arterial wave propagation phenomena, ventricular work, and power dissipation. Ann Biomed Eng 23:804–811
26. Grignola JC, Gines F, Bia D, Armentano R (2007) Improved right ventricular-vascular coupling during active pulmonary hypertension. Int J Cardiol 115:171–182
27. Mesquida J, Gruartmoner G, Espinal C (2013) Skeletal muscle oxygen saturation (StO2) measured by near-infrared spectroscopy in the critically ill patients. BioMed research international 2013: 502194
28. Sabbah HN, Khaja F, Brymer JF, McFarland TM, Albert DE, Snyder JE, Goldstein S, Stein PD (1986) Noninvasive evaluation of left ventricular performance based on peak aortic blood acceleration measured with a continuous-wave Doppler velocity meter. Circulation 74:323–329
29. Fitzmaurice GM, Laird NM, Ware JH (2011) Modeling the covarianceApplied longitudinal analyss. Wiley, Hoboken, pp 165–188

30. de Courson H, Boyer P, Grobost R, Lanchon R, Sesay M, Nouette-Gaulain K, Futier E, Biais M (2019) Changes in dynamic arterial elastance induced by volume expansion and vasopressor in the operating room: a prospective bicentre study. Ann Intensiv Care 9:117
31. Cherpanath TG, Smeding L, Lagrand WK, Hirsch A, Schultz MJ, Groeneveld JA (2014) Pulse pressure variation does not reflect stroke volume variation in mechanically ventilated rats with lipopolysaccharide-induced pneumonia. Clin Exp Pharmacol Physiol 41:98–104
32. Burton AC (1972) Physiology and biophysics of the circulation; an introductory text. Year Book Medical Publishers, Chicago
33. Nichols WW, O'Rourke MF, Avolio AP, Yaginuma T, Pepine CJ, Conti CR (1986) Ventricular/vascular interaction in patients with mild systemic hypertension and normal peripheral resistance. Circulation 74:455–462
34. Cox RH (1974) Determinants of systemic hydraulic power in unanesthetized dogs. Am J Physiol 226:579–587
35. Cholley BP, Lang RM, Berger DS, Korcarz C, Payen D, Shroff SG (1995) Alterations in systemic arterial mechanical properties during septic shock: role of fluid resuscitation. Am J Physiol 269:H375–H384
36. Nichols WW, Conti CR, Walker WE, Milnor WR (1977) Input impedance of the systemic circulation in man. Circ Res 40:451–458
37. Laskey WK, Kussmaul WG, Martin JL, Kleaveland JP, Hirshfeld JW Jr, Shroff S (1985) Characteristics of vascular hydraulic load in patients with heart failure. Circulation 72:61–71
38. Kelly RP, Tunin R, Kass DA (1992) Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ventricle. Circ Res 71:490–502
39. Ince C (2015) Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care 19(Suppl 3):S8
40. Hernandez G, Teboul JL (2016) Is the macrocirculation really dissociated from the microcirculation in septic shock? Intensive Care Med 42:1621–1624
41. Suga H, Hayashi T, Shirahata M (1981) Ventricular systolic pressure-volume area as predictor of cardiac oxygen consumption. Am J Physiol 240:H39–H44
42. Monge Garcia MI, Jian Z, Settels JJ, Hatib F, Cecconi M, Pinsky MR (2018) Reliability of effective arterial elastance using peripheral arterial pressure as surrogate for left ventricular end-systolic pressure. Journal of clinical monitoring and computing
43. Jianhui L, Rosenblatt-Velin N, Loukili N, Pacher P, Feihl F, Waeber B, Liaudet L (2010) Endotoxin impairs cardiac hemodynamics by affecting loading conditions but not by reducing cardiac inotropism. Am J Physiol Heart Circ Physiol 299:H492–H501
44. Pinsky MR, Rico P (2000) Cardiac contractility is not depressed in early canine endotoxic shock. Am J Respir Crit Care Med 161:1087–1093
45. Monge Garcia MI, Romero MG, Cano AG, Rhodes A, Grounds RM, Cecconi M (2013) Impact of arterial load on the agreement between pulse pressure analysis and esophageal Doppler. Crit Care 17:R113

Tables

Table 1. Global hemodynamic changes during the experiment

Variables	Baseline*	1h	2h	3h	4h[a]	*time interaction*	*group interaction*	*group and time interaction*
CO, l/min								
SHAM	0.49 ± 0.06	0.51 ± 0.03	0.54 ± 0.03	0.58 ± 0.05	0.59 ± 0.10	0.057	vs EDX†	< 0.001
EDX	0.54 ± 0.06	0.56 ± 0.07	0.70 ± 0.07	0.83 ± 0.07	0.81 ± 0.09	< 0.001	vs EDX-R†	
EDX-R	0.51 ± 0.08	0.61 ± 0.10	0.77 ± 0.07	0.99 ± 0.14	1.04 ± 0.12	< 0.001	vs SHAM†	
SV, ml								
SHAM	2.7 ± 0.4	2.7 ± 0.3	2.9 ± 0.4	3.1 ± 0.4	3.0 ± 0.6	0.176		0.147
EDX	3.0 ± 0.5	2.8 ± 0.5	3.2 ± 0.7	3.5 ± 0.8	3.5 ± 0.7	0.060		
EDX-R	3.0 ± 0.4	3.4 ± 0.5	3.6 ± 0.5	4.3 ± 0.6	4.1 ± 0.6	0.005		
SAP, mmHg								
SHAM	87 ± 13	76 ± 8	69 ± 10	65 ± 7	61 ± 6	0.010	vs EDX†	< 0.001
EDX	82 ± 11	62 ± 11	50 ± 11	42 ± 4	42 ± 5	0.002	vs EDX-R†	
EDX-R	85 ± 13	61 ± 11	57 ± 7	50 ± 8	77 ± 10	< 0.001	vs SHAM	
DAP, mmHg								
SHAM	53 ± 6	46 ± 6	43 ± 7	40 ± 4	38 ± 3	0.006	vs EDX†	< 0.001
EDX	48 ± 6	41 ± 7	32 ± 6	27 ± 3	26 ± 3	0.007	vs EDX-R	
EDX-R	48 ± 7	37 ± 5	35 ± 3	29 ± 3	47 ± 6	< 0.001	vs SHAM†	
MAP, mmHg								
SHAM	63 ± 7	55 ± 6	51 ±8	47 ± 5	46 ± 3	0.006	vs EDX†	< 0.001
EDX	57 ± 7	47 ± 8	38 ± 8	34 ± 1	30 ± 3	0.007	vs EDX-R†	
EDX-R	58 ± 8	45 ± 7	42 ± 4	38 ± 3	59 ± 5	< 0.001	vs SHAM†	

Data are presented as mean ± standard deviation. CO: cardiac output; DAP: diastolic arterial pressure; HR: heart rate; MAP: mean arterial pressure; SAP: systolic arterial pressure; SV: stroke volume.

SHAM: sham-operated group; EDX: non-resuscitated septic rabbits; EDX-R: resuscitated septic rabbits.

* Baseline values were similar between different experimental groups.

[a] In the EDX-R group, 4h refers after both fluid bolus and norepinephrine infusion.

† $p < 0.05$ for between-group effects (Tukey-Kramer).

Table 2. Arterial variables during different stages of the experiment

Variables	Baseline*	1h	2h	3h	4h[a]	*time interaction*	*group interaction*	*group and time interaction*
Arterial load variables								
Ea, mmHg/ml·10^{-1}								
SHAM	0.83 ± 0.18	0.52 ± 0.09	0.43 ± 0.09	0.34 ± 0.04	0.36 ± 0.11	0.001		0.769
EDX	0.67 ± 0.29	0.39 ± 0.16	0.22 ± 0.08	0.16 ± 0.02	0.14 ± 0.01	0.021		
EDX-R	0.68 ± 0.23	0.31 ± 0.09	0.23 ± 0.05	0.16 ± 0.04	0.24 ± 0.05	0.001		
C, mL/mmHg								
SHAM	0.08 ± 0.02	0.09 ± 0.01	0.11 ± 0.03	0.13 ± 0.02	0.13 ± 0.02	0.006	vs EDX†	0.001
EDX	0.09 ± 0.02	0.13 ± 0.03	0.19 ± 0.05	0.23 ± 0.04	0.31 ± 0.04	< 0.001	vs EDX-R	
EDX-R	0.08 ± 0.02	0.15 ± 0.04	0.17 ± 0.06	0.21 ± 0.06	0.14 ± 0.03	< 0.001	vs SHAM†	
Zc, dyn·s·cm^{-5}·10^{3}								
SHAM	0.81 ± 0.24	0.70 ± 0.17	0.58 ± 0.17	0.49 ± 0.15	0.52 ± 0.20	0.013	vs EDX†	0.020
EDX	0.84 ± 0.13	0.52 ± 0.11	0.35 ± 0.06	0.23 ± 0.03	0.18 ± 0.04	0.001	vs EDX-R	
EDX-R	0.85 ± 0.22	0.47 ± 0.10	0.39 ± 0.08	0.31 ± 0.12	0.45 ± 0.07	0.001	vs SHAM	
SVR, dyn·s·cm^{-5}·10^{3}								
SHAM	10.55 ± 1.98	6.52 ± 1.01	5.72 ± 0.93	4.85 ± 0.33	4.87 ± 1.01	<0.001		0.535
EDX	8.66 ± 2.18	5.25 ± 1.68	3.25 ± 0.97	2.48 ± 0.19	2.25 ± 0.12	0.004		
EDX-R	9.37 ± 2.52	4.52 ± 1.04	3.31 ± 0.45	2.32 ± 0.35	3.42 ± 0.50	<0.001		
Cardiac variables								
HR, beats/min								
SHAM	180 ± 28	187 ± 26	191 ± 24	188 ± 21	197 ± 24	0.039	vs EDX†	< 0.001
EDX	182 ± 20	202 ± 22	222 ± 29	243 ± 39	237 ± 39	0.014	vs EDX-R	
EDX-R	169 ± 17	178 ± 15	217 ± 40	234 ± 41	256 ± 18	0.004	vs SHAM†	
Accel, m/s^{2}								
SHAM	6.47 ± 0.87	6.55 ± 0.47	6.58 ± 0.54	7.09 ± 0.58	7.02 ± 1.07	0.303		0.057
EDX	6.41 ± 0.69	6.19 ± 0.84	6.81 ± 0.39	7.29 ± 1.00	6.70 ± 0.77	0.107		
EDX-R	6.95 ±	6.87 ±	7.51 ±	8.93 ±	8.96 ±	0.018		

	0.81	0.92	0.59	.03	1.42

Data are presented as mean ± standard deviation.

Accel: mean acceleration of aortic blood flow; C: net arterial compliance; Ea: effective arterial elastance; HR: heart rate; SVR: systemic vascular resistance; Zc: characteristic impedance.

SHAM: sham-operated group; EDX: septic group without hemodynamic resuscitation; EDX-R: hemodynamic resuscitated septic group.

* Baseline values were similar between different experimental groups.

[a] In the EDX-R group, 4h refers after hemodynamic resuscitation (both fluid bolus and norepinephrine infusion).

† $p < 0.05$ for between-group effects (Tukey-Kramer).

Table 3. Effects of fluid bolus and norepinephrine in hemodynamic, tissue oxygenation, arterial variables and cardiac energetics in resuscitated septic animals (EDX-R group)

	3h post-LPS	After fluid bolus (20 mL/Kg)	After norepinephrine (4h post-LPS)
Hemodynamic variables			
CO, l/min^{-1}	0.99 ± 0.14	1.16 ± 0.09*	1.04 ± 0.12*†
SV, ml	4.3 ± 0.6	4.7 ± 0.6*	4.1 ± 0.6
SAP, mmHg	50 ± 8	61 ± 10*	77 ± 10*†
DAP, mmHg	29 ± 3	35 ± 2*	47 ± 6*†
MAP, mmHg	38 ± 3	45 ± 4*	59 ± 5*†
SVV, %	22 ± 4	20 ± 3	24 ± 3†
PPV, %	30 ± 7	19 ± 7*	21 ± 6*
Ea_{dyn}	1.38 ± 0.32	0.93 ± 0.24*	0.87 ± 0.15*
Arterial variables			
Ea, $mmHg/mL \cdot 10^{-1}$	0.16 ± 0.04	0.15 ± 0.03	0.24 ± 0.05
C, ml/mmHg	0.21 ± 0.06	0.19 ± 0.07	0.14 ± 0.03
Zc, $dyn \cdot s \cdot cm^{-5} \cdot 10^3$	0.31 ± 0.12	0.35 ± 0.13	0.45 ± 0.07
SVR, $dyn \cdot s \cdot cm^{-5} \cdot 10^3$	2.32 ± 0.35	2.32 ± 0.27	3.42 ± 0.50*†
Cardiac variables			
HR, beats/min	234 ± 41	251 ± 25	256 ± 18
Accel, m/s^2	8.93 ± 1.03	9.91 ± 0.63	8.96 ± 1.42
Cardiac energetics			
$\dot{W}_{tot}$, mW	87 ± 12	128 ± 19*	152 ± 22*†
$\dot{W}_{std}$, mW	80 ± 10	115 ± 16*	137 ± 20*†
$\dot{W}_{osc}$, mW	7 ± 2	13 ± 4	16 ± 2*
%Osc, %	9 ± 2	10 ± 2	10 ± 1*
EER, $mW \cdot min \cdot ml^{-1}$	0.09 ± 0.01	0.11 ± 0.01	0.15 ± 0.01*†
Tisular perfusion variables			
StO_2, %	44.1 ± 5.2	49.6 ± 4.6*	50.4 ± 6.8
Mmi, W/%	2.00 ± 0.28	2.60 ± 0.45*	3.07 ± 0.67*†

Data are presented as mean ± standard deviation.

Accel: maximal acceleration of aortic blood flow; C: net arterial compliance; CO: cardiac output; DAP: diastolic arterial pressure; Ea: effective arterial elastance; Ea_{dyn}: dynamic arterial elastance; EER: energy efficiency ratio ($\dot{W}_{tot}/CO$); HR: heart rate; LPS: lipopolysaccharide; MAP: mean arterial pressure; Mmi: macro-microcirculatory index ($\dot{W}_{total}/StO_2$); PPV: arterial pulse pressure variation; SAP: systolic arterial pressure; StO_2: tisular oxygen saturation; SV: stroke volume; SVV: stroke volume variation; SVR: systemic vascular resistance; $\dot{W}_{osc}$: left ventricular oscillatory power; $\dot{W}_{std}$: left ventricular steady power; $\dot{W}_{tot}$: left ventricular total power; Zc: characteristic impedance; %Osc: oscillatory power fraction ($\dot{W}_{osc}/\dot{W}_{tot}$).

* $p < 0.05$ vs *3h postLPS* stage, † $p < 0.05$ vs *After fluid bolus* stage (Bonferroni corrected).

Table 4. Relationship between Ea_{dyn} and arterial load, cardiac variables, cardiac energetics, LV efficiency and peripheral perfusion indexes according to a mixed-effect regression model in septic animals (EDX and EDX-R).

Fixed effects	Estimate (95% confidence interval)	p value
Arterial load		
SVR, $dyn{\cdot}s{\cdot}cm^{-5}{\cdot}10^{3}$	0.009 (-0.056 – 0.075)	0.770
C, ml/mmHg	0.509 (-1.534 – 2.552)	0.611
Zc, $dyn{\cdot}s{\cdot}cm^{-5}{\cdot}10^{3}$	-1.053 (-1.896 – -0.209)	0.017
Cardiac variables		
Heart rate, beats/min	0.006 (0.003 – 0.008)	<0.001
Accel, ms/s^{2}	0.047 (-0.044 – 0.137)	0.301
Cardiac energetics		
$\dot{W}_{std}$, W	0.017 (0.007 – 0.027)	<0.001
$\dot{W}_{osc}$, W	-0.125 (-0.174 – -0.076)	<0.001
Cardiovascular efficiency		
%Osc	-0.101 (-0.137 – -0.064)	<0.001
EER, $W{\cdot}s{\cdot}ml^{-1}$	-9.494 (-11.964 – -7.024)	<0.001

Accel: maximal acceleration of aortic blood flow; C: arterial compliance; Ea_{dyn}: dynamic arterial elastance; EER: energy efficiency ratio; Mmi: macro-microhemodynamic coupling index (W_{tot}/StO_2); PV: peak velocity of aortic blood flow; SVR: systemic vascular resistance; StO_2: tissular oxygen saturation; $\dot{W}_{osc}$: left ventricular oscillatory work; $\dot{W}_{std}$: left ventricular steady work; Zc: characteristic impedance; %Osc: oscillatory power fraction.

Estimates reflect the average change in Ea_{dyn} per unit increase of the fixed covariate. Mixed-effect regression models were constructed using arterial variables (SVR, C and Zc), cardiac variables (HR and Accel), cardiac energetic variables ($\dot{W}_{std}$ and $\dot{W}_{osc}$), %Osc, EER, as independent variables.

Figures

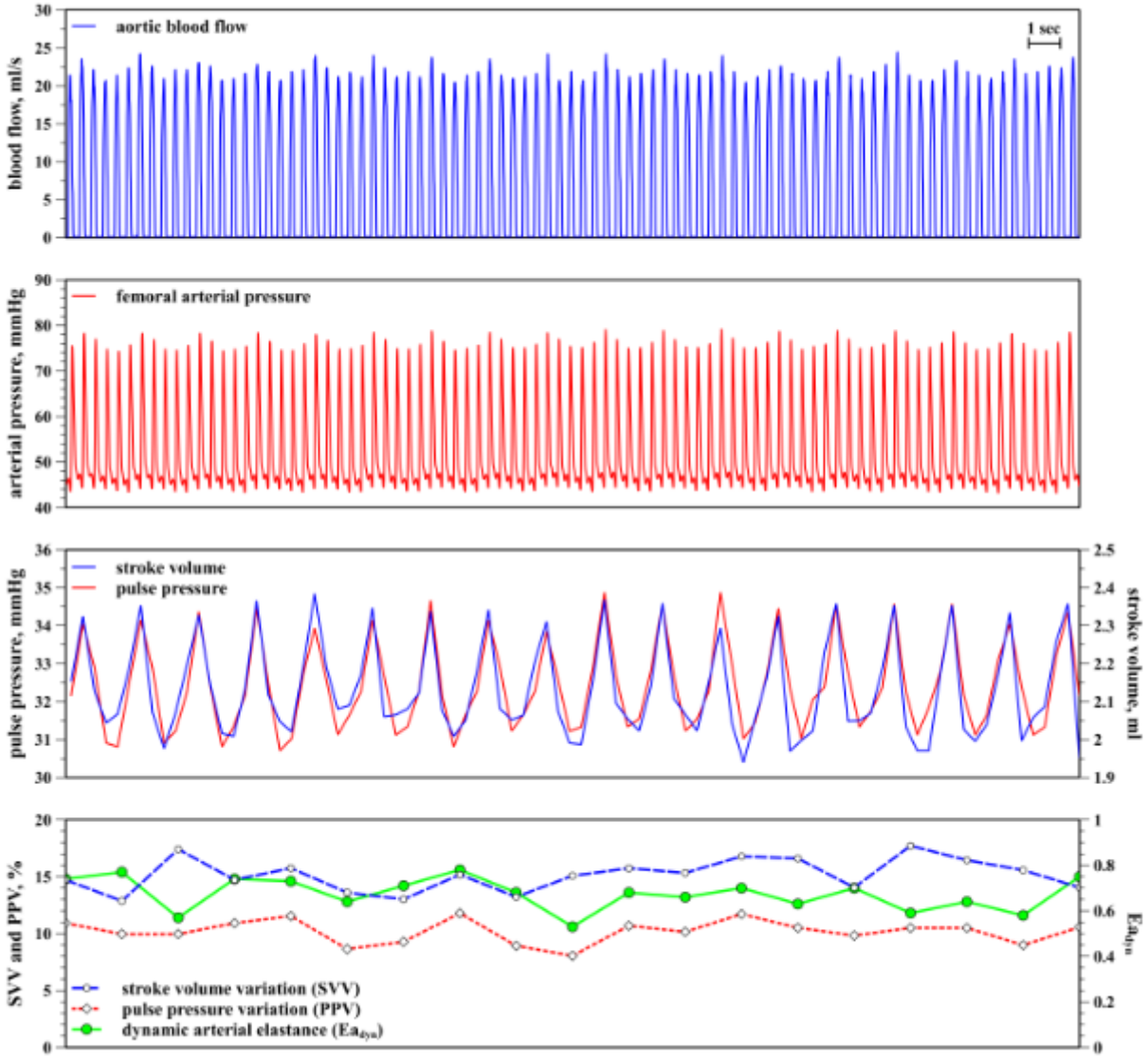

Figure 1

Calculation of pulse pressure variation (PPV), stroke volume variation (SVV), and dynamic arterial elastance (Eadyn). From top to bottom: aortic blood flow (blue); femoral arterial pressure (red); beat-to-beat stroke volume and arterial pulse pressure (pink and dark blue); stroke volume variation (SVV, dotted red line), pulse pressure variation (PPV, blue dashed line) and dynamic arterial elastance (Eadyn, solid green line).

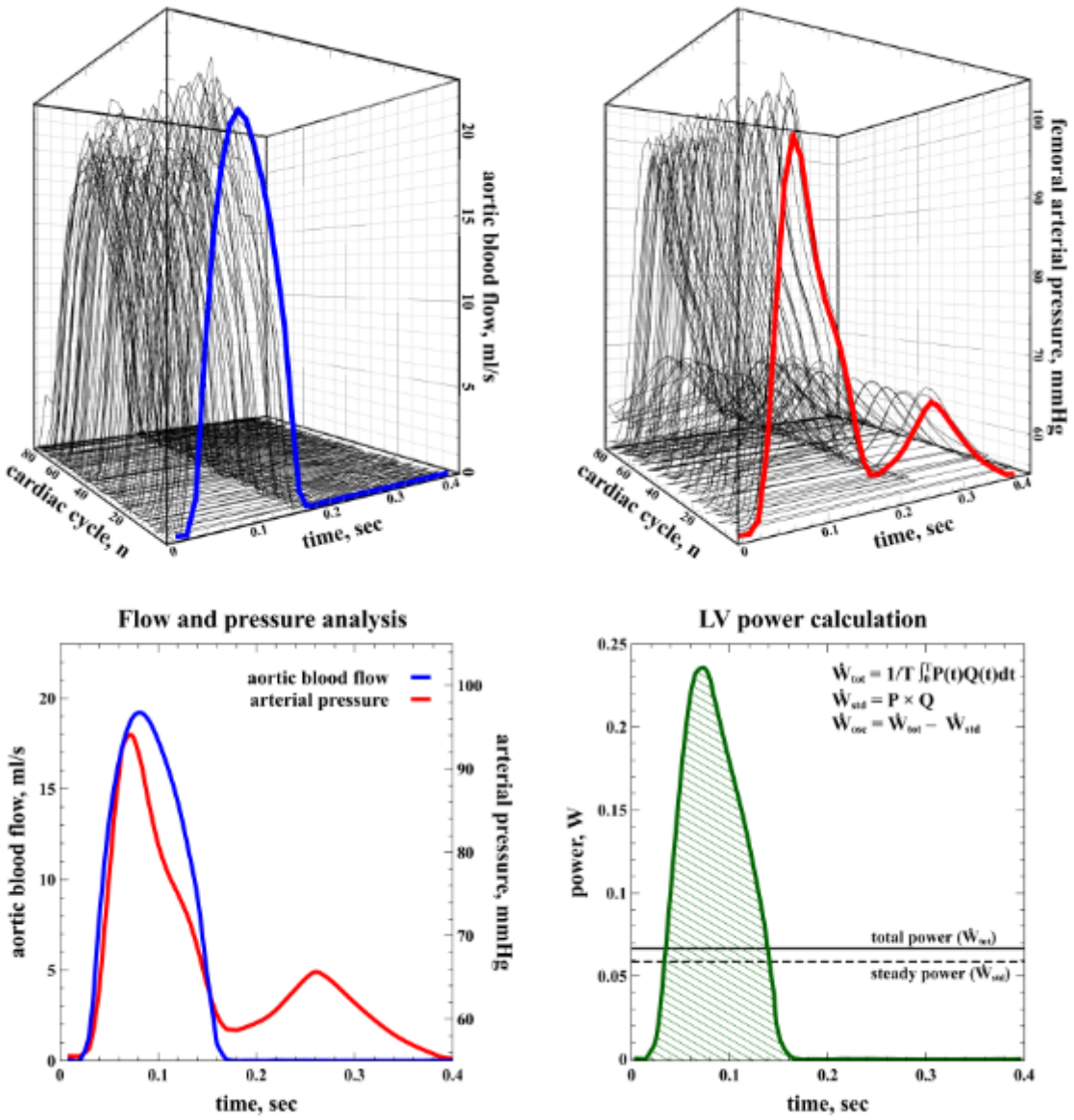

Figure 2

Calculation of left ventricular energetics. Aortic blood flow (top left, blue line) and arterial pressure waveforms (top right, red line) were ensembled-averaged (bottom, left) for analysis. The total LV power (Ẇtot) transferred to the systemic circulation was calculated as the time-averaged integral of the instantaneous product of pressure and flow during the whole cardiac period (bottom right, green shaded area). The difference between total power (Ẇtot) and steady power (Ẇstd, solid line) represents the extra expenditure of energy imposed by the pulsatile nature of the heart, i.e., the oscillatory power (Ẇosc, dashed line).

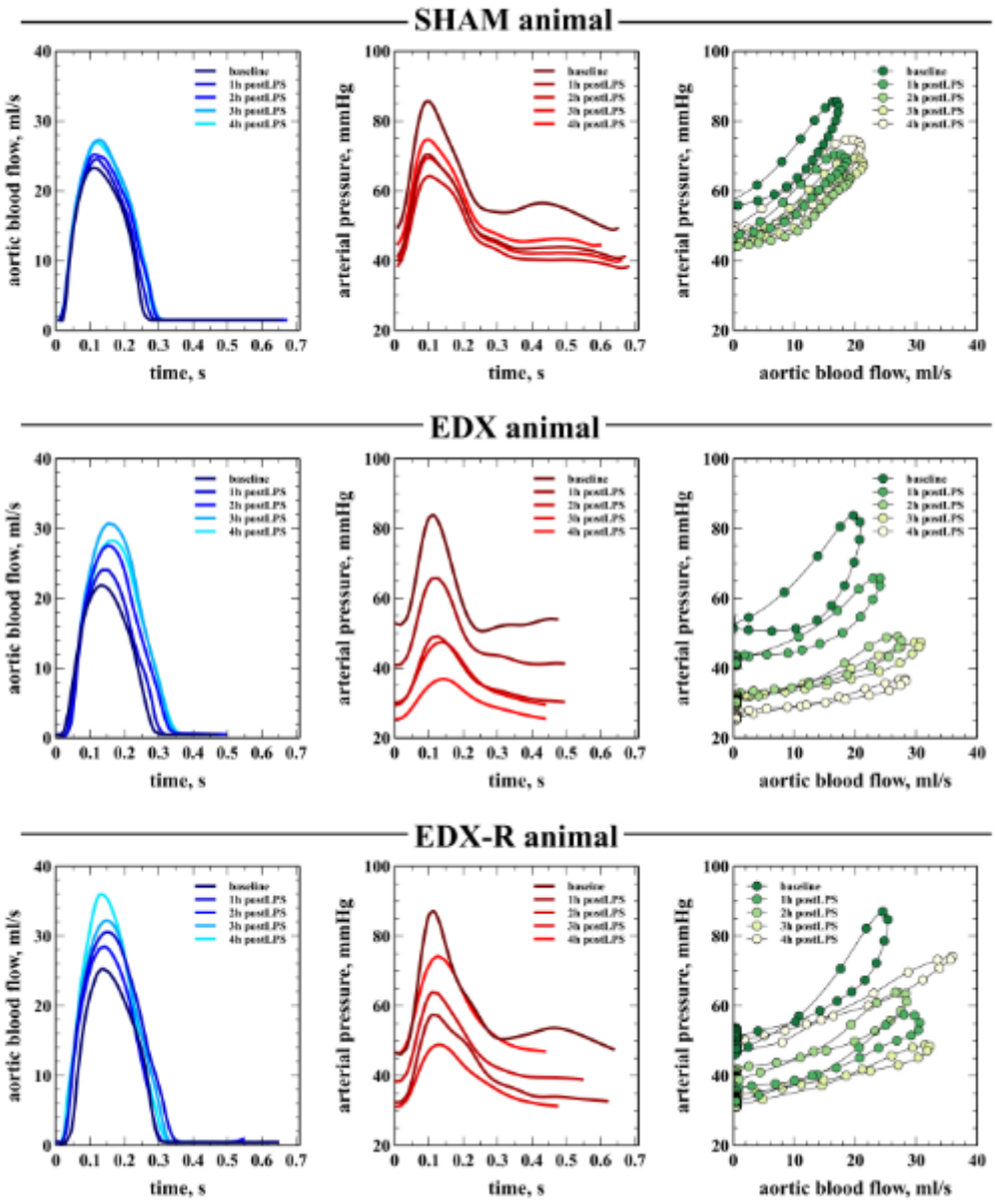

Figure 3

Evolution of arterial pressure-flow relationship. Example of the evolution of blood flow (left column) and arterial pressure waveform (middle column) and the pressure-flow loops (right column) in three animals from sham-operated group (SHAM), endotoxic group (EDX), and hemodynamic-resuscitated endotoxic group (EDX-R) during the study. In this latter group, 4h stage refers to after both fluid bolus and norepinephrine infusion. Pressure-flow loops were constructed using data form the shown aortic blood flow and arterial pressure waveforms on each experimental stage.

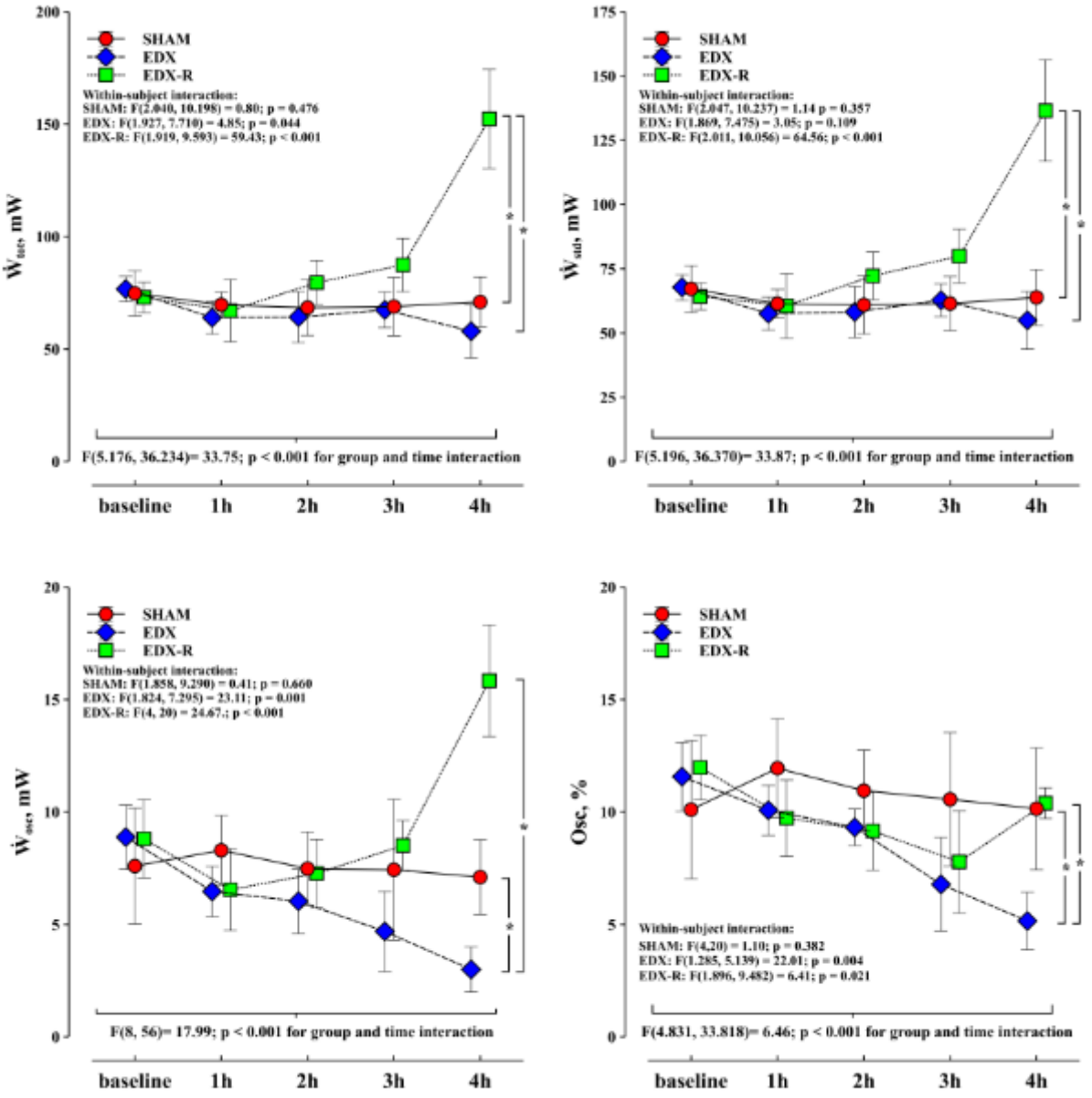

Figure 4

Evolution of left ventricular energetics. Changes in left ventricular total work (Ẇtot), steady power (Ẇstd), oscillatory power (Ẇosc) and oscillatory power fraction (Osc) in the three experimental groups: Experimental arms: sham-operated group (SHAM), resuscitated endotoxic group (EDX), and hemodynamic-resuscitated group (EDX-R). Values are presented as mean ± SD. Differences in time course between groups: * p < 0.05.

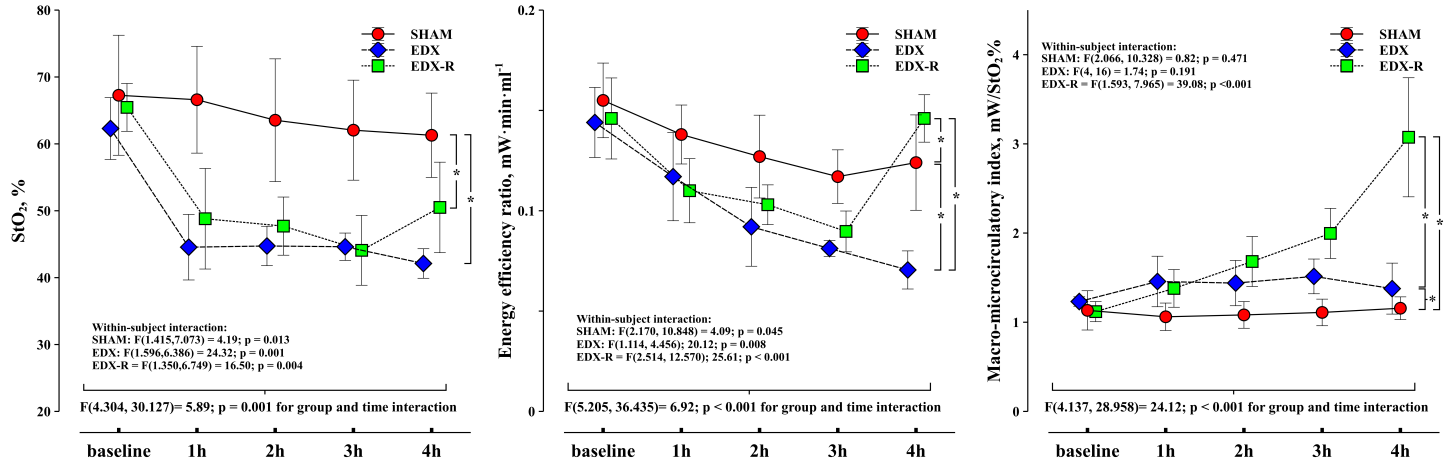

Figure 5

Evolution of tissue oxygen saturation (StO2), energy efficiency ratio (EER) and macro-microcirculatory coupling index (Mmi). Experimental arms: sham-operated group (SHAM), resuscitated endotoxic group (EDX), and hemodynamic-resuscitated group (EDX-R). Values are presented as mean ± SD. Differences in time course between groups: * p < 0.05.

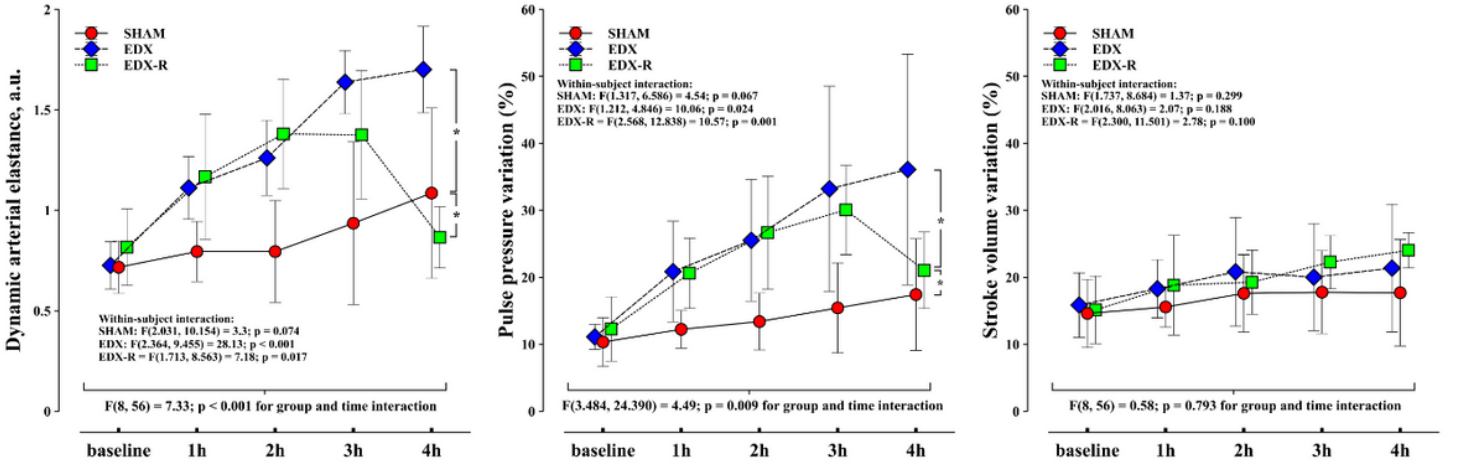

Figure 6

Evolution of dynamic arterial elastance, pulse pressure variation (PPV) and stroke volume variation (SVV). Experimental arms: sham-operated group (SHAM), resuscitated endotoxic group (EDX), and hemodynamic-resuscitated group (EDX-R). Values are presented as mean ± SD. Differences in time course between groups: * p < 0.05.

Supplementary Files

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