

COMMENTARY

Weighing the evidence for using vascular conductance, not resistance, in comparative cardiovascular physiology

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ABSTRACT

Vascular resistance and conductance are reciprocal indices of vascular tone that are often assumed to be interchangeable. However, in most animals *in vivo*, blood flow (i.e. cardiac output) typically varies much more than arterial blood pressure. When blood flow changes at a constant pressure, the relationship between conductance and blood flow is linear, whereas the relationship between resistance and blood flow is non-linear. Thus, for a given change in blood flow, the change in resistance depends on the starting point, whereas the attendant change in conductance is proportional to the change in blood flow regardless of the starting conditions. By comparing the effects of physical activity at different temperatures or between species – concepts at the heart of comparative cardiovascular physiology – we demonstrate that the difference between choosing resistance or conductance can be marked. We also explain here how the ratio of conductance in the pulmonary and systemic circulations provides a more intuitive description of cardiac shunt patterns in the reptilian cardiovascular system than the more commonly used ratio of resistance. Finally, we posit that, although the decision to use conductance or resistance should be made on a case-by-case basis, in most circumstances, conductance is a more faithful portrayal of cardiovascular regulation in vertebrates.

KEY WORDS: Exercise, Cardiac shunting, Cardiac output, Vasodilation

Introduction

The control of peripheral vascular tone (see Glossary) is paramount for the regulation of cardiac output by virtue of altering vascular resistance or conductance (see Glossary) to match blood flow to metabolic demands (Bada et al., 2012; González-Alonso et al., 2008; Guyton, 1968; Joyce et al., 2019). Conductance (blood flow/ Δ pressure) is the reciprocal of resistance (Δ pressure/blood flow), and these two indices are widely assumed to be interchangeable. By convention – or at least without explicit justification – resistance has typically been favoured amongst comparative cardiovascular physiologists (e.g. Altimiras and Axelsson, 2004; Axelsson et al., 1992; Blix, 2018; Crossley et al., 1998; Ekström et al., 2016; Gamperl et al., 2011; Keen et al., 2016; Mendonça and Gamperl, 2009; Sandblom et al., 2005). However, it has long been recognised within the mammalian (i.e. biomedical) literature that an arbitrary decision can lead to numerous pitfalls (Lautt, 1989; O’Leary, 1991;

Stark, 1968). Our aim here is to explain why the distinction between resistance and conductance is particularly pertinent in comparative cardiovascular physiology. To this end, we rely on comparative studies published in the *Journal of Experimental Biology* to illustrate our arguments. In the first example, we compare the effects of physical activity at different temperatures in a fish (Joyce et al., 2018a), a type of study that is burgeoning in the current era of ‘conservation physiology’, demonstrating how the selection of resistance or conductance can fundamentally alter the conclusions of a study. In the second example, we demonstrate how the choice of index is important when comparing the effects of exercise across species (pigeons: Butler et al., 1977; and emus: Grubb et al., 1983), a type of analysis that is, by definition, at the heart of comparative physiology. Finally, we compare the use of ratios of conductance or resistance of the pulmonary and systemic circulation (see Glossary) in reptiles with an undivided ventricle to describe the control of intracardiac shunts (see Glossary; Crossley et al., 1998). We begin by highlighting the theoretical distinction between resistance and conductance.

What are resistance and conductance?

Mathematically, resistance is the inverse of conductance. The behaviour of blood flow in an isolated vessel, vascular bed or the entire circulation resembles an electrical circuit; where resistance typically remains constant, the voltage change (ΔV) is linearly related to both current (I) and resistance, as expressed by Ohm’s law: $V=IR$. Current, by contrast, is linearly related to both voltage (V) and conductance ($G=1/R$), therefore $I=VG$. Physiologists apply Ohm’s law to describe haemodynamic states, but typically substitute the pressure difference across the vessel or vascular bed (ΔP) for the voltage change (ΔV), and substitute blood flow (\dot{Q}) for the current (I) to yield the familiar description of $\Delta P=\dot{Q}R$, where R , as within an electrical circuit, represents resistance. However, in contrast to electrical circuits where resistance (and conductance) normally remains constant, all three of the variables (ΔP , \dot{Q} and R) can readily alter in living systems because of attendant changes in vascular tone. Thus, the hydrostatic flow–pressure relationships that exist in rigid tubes with fixed diameter, or in electrical circuits with fixed resistance, become imprecise analogies during conditions of high or low flow in the cardiovascular system. Furthermore, when the blood vessels constrict or dilate in response to local endogenous metabolites, stress–relaxation influences or exogenous neuro-endocrine or pharmaceutical influences, a meaningful change in vascular tone is more easily identified when the change in flow is expressed as the per unit change in pressure (ΔP) – that is, conductance.

Cardiac output (systemic blood flow) is regulated to meet oxygen demands, and can vary severalfold depending on the metabolic state of a given animal (Hedrick et al., 2015; Hillman and Hedrick, 2015). By contrast, arterial blood pressure changes relatively little between rest and exercise (Magder, 2018; Munch et al., 2014; Sandblom

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Glossary**Baroreflex**

The homeostatic mechanism that maintains a relatively constant arterial blood pressure.

Intracardiac shunt

The recirculation of oxygen-poor blood to the systemic circulation (right-to-left shunting) or oxygen-rich blood to the pulmonary circulation (left-to-right shunting) due to mixing of blood in the heart.

Pulmonary circulation

The pulmonary arteries, capillaries and veins, which carry oxygen-poor blood to the lungs and return oxygen-rich blood to the left atrium.

Systemic circulation

The systemic arteries, capillaries and veins which supply the body with oxygen-rich arterial blood and return oxygen-poor blood to the right atrium.

Vascular conductance

The ease with which blood flows through a circulation (or vascular bed) at a given pressure difference (the reciprocal of resistance).

Vascular resistance

The hindrance to blood flow in a circulation (or a vascular bed) at a given pressure difference (the reciprocal of conductance).

Vascular tone

The degree of constriction of a given blood vessel, vascular bed or circulation.

et al., 2005). Indeed, the baroreflex (see Glossary) represents an exquisitely tuned homeostatic mechanism to maintain a near-constant blood pressure in vertebrates (Raven et al., 2006; Van Vliet and West, 1994).

In a hypothetical example, when blood flow changes at constant arterial and venous pressure, the relationship between conductance (the numerator) and blood flow is linear, whereas the relationship between resistance (the denominator) and blood flow is non-linear (Fig. 1). Thus, at low flow rates, a given change in flow is associated with a very large change in resistance (situation A; Fig. 1), whereas the same change at higher baseline flow rates is associated with a 12 times smaller change in resistance in this theoretical example provided in situation B (Fig. 1). By contrast, the change in conductance is proportional to the change in blood flow, irrespective of the starting point (Fig. 1).

An intraspecific example – the effects of activity at two temperatures

In a recently published study on the Antarctic icefish *Chaenocephalus aceratus*, which do not express haemoglobin, Joyce and colleagues (2018a) reported the effects of physical activity on cardiac output and dorsal aortic pressure at three temperatures (0.8, 4 and 8°C) (Joyce et al., 2018a). Data from this study are replotted in Fig. 2, where central venous pressure is assumed to be negligible when calculating the pressure gradient. At the highest and lowest temperatures, cardiac output changes by approximately the same magnitude from rest to activity (15.4 or 14.0 ml min⁻¹ at 0 and 8°C, respectively). However, because the resting blood flow at high temperature is on the plateauing portion of the resistance curve (Fig. 2A), the large change in blood flow is associated with a very small change in resistance. Indeed, using a conventional repeated-measures two-way ANOVA accompanied by Sidak's *post hoc* test, although there are significant ($P < 0.05$) decreases in resistance at lower temperatures, there is no statistically significant change in resistance from rest to activity at 8°C ($P = 0.13$; Fig. 2B). By contrast, there is an almost linear relationship between blood flow and conductance (Fig. 2C), despite the small decrease in dorsal aortic pressure (from approximately 1.8 to 1.3 kPa) with

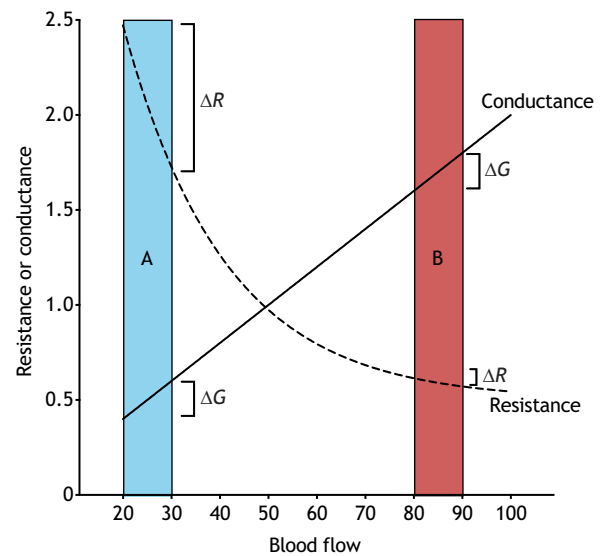


Fig. 1. The hypothetical relationship between vascular conductance, and resistance, and blood flow when the pressure gradient does not change, as in the cardiovascular system of most vertebrates. Situations A and B are cases in which blood flow changes by the same amount (10 a.u.). However, in case A, resistance changes 12-fold more than in case B. Conductance, meanwhile, changes by the same magnitude, and so is not sensitive to the starting condition and is proportional to the change in blood flow. Units are arbitrary (a.u.) and illustrative only. Vertical brackets highlight the change in resistance (ΔR) or change in conductance (ΔG) in each situation.

increasing temperature (Joyce et al., 2018a). This means that the change in vascular conductance from rest to activity is similar, and always statistically significant, across temperatures (Fig. 2D), unlike the situation for resistance.

Thus, based on the above analysis, choosing resistance as the index to describe the physiological responses would lead to the erroneous (albeit fashionable) conclusion that the regulation of vascular tone is compromised at high temperature. This is clearly not the case – not only was the increase in flow similar at 0 and 8°C but also dorsal aortic pressure essentially did not change from rest to activity at 0°C, instead exhibiting a small, albeit significant ($P < 0.05$), decrease (~ 0.1 kPa) at 8°C, despite the elevation in blood flow (Joyce et al., 2018a). Thus, conductance clearly provides a more faithful representation of the change in vascular status compared with resistance.

An interspecific example – the effects of activity in two species of birds

As within individual animals, arterial pressure is also regulated within relatively narrow limits within species belonging to the same taxonomic class, especially within endotherms (mammals and birds), in which it is striking that blood pressure tends to increase only slightly, or not at all, with body mass (Poulsen et al., 2018; Seymour and Blaylock, 2000; White and Seymour, 2014). Larger animals obviously require a greater absolute cardiac output; thus, when comparing animals of different sizes, we have a situation where blood flow ‘changes’ (between species) much more than the pressure gradient. This problem is compounded when the effects of exercise are considered, because, just like in ectotherms, in birds and mammals arterial pressure changes very little from the resting state (Butler et al., 1977; Grubb, 1982; Grubb et al., 1983; Munch et al., 2014).

Birds provide a prime example as they show little variation in blood pressure, but can exhibit very large changes in cardiac output,

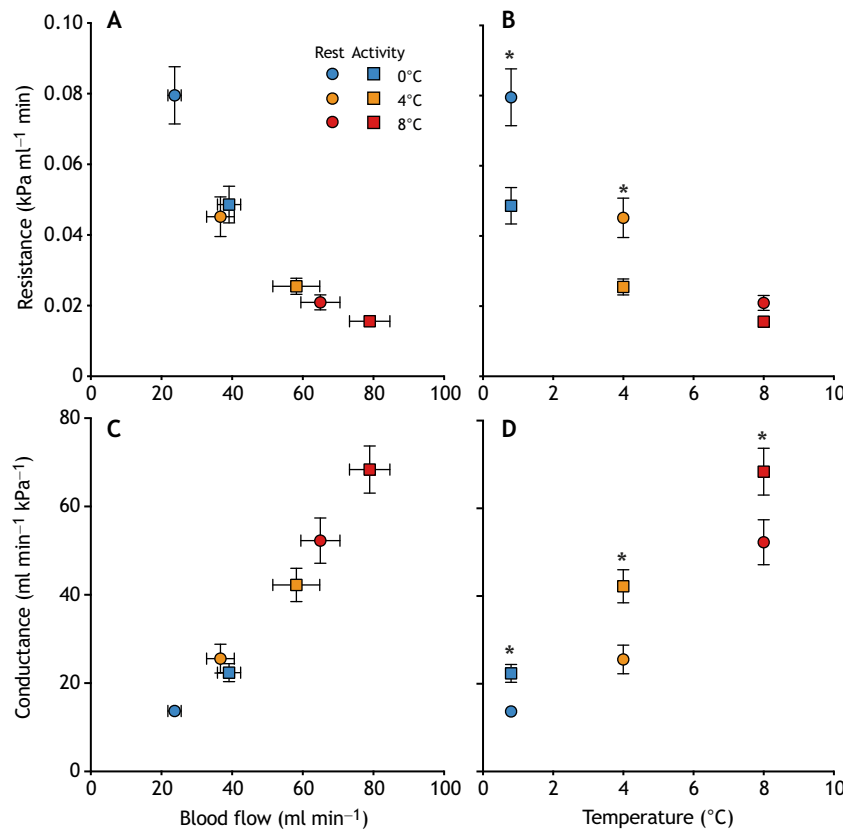


Fig. 2. Effects of activity at different temperatures in the icefish *Chaenocephalus aceratus*. Data are from Joyce et al. (2018a). Body mass: 0.86 ± 0.18 kg (mean \pm s.d.). (A) The relationship between resistance and blood flow is non-linear and plateaus at high flow rates. (B) Resistance is significantly lower during activity than at rest only at 0.8 and 4°C, but not at 8°C. (C) However, the relationship between conductance and blood flow is approximately linear. (D) It is clear that conductance is significantly higher during activity than at rest across all assessed temperatures.

for example during running (particularly in ratites) or flight. To provide an example, we compare the effects of treadmill exercise in the emu (*Dromaius novaehollandiae*; Grubb et al., 1983) with flight in the pigeon (*Columba livia*; Butler et al., 1977). Emus have a 10-fold greater resting absolute cardiac output than pigeons (2546 versus 245 ml min^{-1} ; Fig. 3), as would be expected given their much larger body mass (37.5 versus 0.44 kg). Likewise, during exercise, blood flow increases by a greater absolute magnitude in the emu than in the pigeon (Fig. 3). Because arterial blood pressure is similar in emus and pigeons (approximately 17 and 19 kPa, respectively) and does not change materially with exercise, the relationships between resistance or conductance and blood flow are essentially as predicted in Fig. 1. Thus, despite exhibiting a much smaller change in absolute cardiac output, exercising pigeons show a paradoxically greater change in resistance than emus (Fig. 3A). By contrast, the changes in conductance in the different species are

proportional to the changes in blood flow (Fig. 3B). Given that this relationship is simply an inevitable mathematical product when blood flow changes at stable pressure, it is relevant across taxa whenever species with similar arterial blood pressure but different cardiac output are compared.

Conductance and resistance ratios – the regulation of cardiac shunts in reptiles and amphibians

Most reptiles (with the exception of crocodiles), as well as amphibians, possess hearts that comprise a single ventricle that supplies both the systemic and pulmonary circulations (Hicks, 2002; Jensen et al., 2013; White, 1968). As a result, the heart is capable of generating large intracardiac shunts, where oxygen-poor blood can re-enter the systemic circulation and bypass the lungs (right-to-left shunt), or oxygenated blood returning from the lungs may recirculate in the pulmonary circulation (left-to-right shunt)

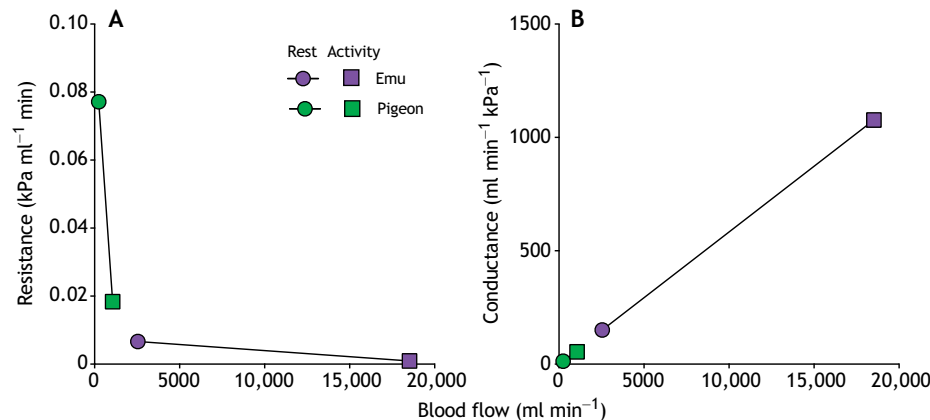


Fig. 3. Relationship between vascular resistance or conductance and absolute blood flow in birds of different sizes during rest and activity. Data are shown for the flightless emu, *Dromaius novaehollandiae* (37.5 kg), running on a treadmill (Grubb et al., 1983); and the pigeon *Columba livia* (0.44 kg), flying in a wind tunnel (Butler et al., 1977). The change in vascular resistance is greater in pigeons than in emus, despite their much smaller absolute change in total blood flow (cardiac output) (A). However, the change in conductance is proportional to the change in blood flow exhibited by the two species (B).

(Joyce et al., 2016; Wang and Hicks, 1996; White, 1968). The direction and magnitude of the intracardiac shunting are variable, but tightly regulated, and change predictably with the physiological state of an animal (Hicks and Wang, 2012). For example, during diving, aquatic species characteristically increase the right-to-left shunt (Lillywhite and Donald, 1989; Millen et al., 1964; White and Ross, 1966; Joyce et al., 2018b) to bypass the unventilated lungs. The pulmonary and systemic vascular tone are regulated by the autonomic nervous system and a suite of other endocrine and paracrine factors (Filogonio et al., 2017; Hicks and Comeau, 1994; Joyce and Wang, 2014; Overgaard et al., 2002; Skovgaard et al., 2005) that alter vascular tone and hence divert blood flow between the two circulations.

To graphically illustrate how the ratio of pulmonary and systemic resistance (R_{pul}/R_{sys}) affects the cardiac shunt ratio – that is, the proportion of blood flow sent to the lungs ($\dot{Q}_{pul}/\dot{Q}_{sys}$) – Crossley et al. (1998) plotted $\dot{Q}_{pul}/\dot{Q}_{sys}$ against R_{pul}/R_{sys} using data from anaesthetised turtles (*Trachemys scripta*) ventilated with a range of hypoxic gas mixtures. These data (replotted in Fig. 4A), which have been independently replicated (Overgaard et al., 2002) and reproduced elsewhere (Hicks and Wang, 2012), neatly illustrate how a high pulmonary resistance, relative to systemic resistance (R_{pul}/R_{sys}) leads to a low relative pulmonary blood flow ($\dot{Q}_{pul}/\dot{Q}_{sys}$) as a result of the hypoxic vasoconstriction of the pulmonary vasculature. However, it is confusing and difficult to reconcile why small changes in R_{pul}/R_{sys} at the low end of the spectrum (i.e. low baseline R_{pul}/R_{sys}) result in huge changes in $\dot{Q}_{pul}/\dot{Q}_{sys}$, whereas $\dot{Q}_{pul}/\dot{Q}_{sys}$ plateaus in the high range of R_{pul}/R_{sys} . To estimate how much of the variability in the cardiac shunts could be accounted for by R_{pul}/R_{sys} , Overgaard and colleagues (2002) linearised a similar dataset (obtained by pharmacological manipulation of vascular tone in the same turtle species) in a double-log scale fitted to a power function. However, this somewhat convoluted method would not be necessary if conductance had been used instead. This is shown in Fig. 4B, where the data of Crossley et al. (1998) have been replotted as a function of the ratio of pulmonary conductance to systemic conductance (G_{pul}/G_{sys}) to yield a linear relationship ($R^2=0.99$) that elegantly depicts how cardiac shunts are controlled by vascular tone in reptiles.

The above example is particularly striking because, in the anaesthetised turtles, hypoxia elicited a large decrease in pulmonary blood flow with no change in mean pulmonary arterial blood pressure (Crossley et al., 1998). Nevertheless, given the normal barostatic regulation of blood pressure in conscious reptiles (e.g. Hagensen et al., 2010), this appears generally applicable across the

class. For example, during diving, it is well known that large changes in blood flow are accompanied by little or no change in arterial pressure (Lillywhite and Donald, 1989; White and Ross, 1966). In analysing data from rattlesnakes (*Crotalus durissus*), Filogonio and colleagues (2016) were the first to report that $\dot{Q}_{pul}/\dot{Q}_{sys}$ correlates linearly with G_{pul}/G_{sys} ($R^2=0.82$) in reptiles. Our side-by-side comparison of R_{pul}/R_{sys} and G_{pul}/G_{sys} demonstrates clearly why the latter produces a simpler and more intuitive illustration that is easier to analyse using linear models that, we contend, should be more widely adopted in cardiovascular studies on reptiles and amphibians. More generally, this principle probably holds true whenever blood flow through two vascular beds (or circulations) is compared within an organism.

Concluding remarks

We have demonstrated that, when comparing the effects of a change in activity at different temperatures or in different species (especially those with different body masses), the outcome of the analysis is sensitive to the choice between resistance and conductance. We hasten to add that, when simple pairwise analyses are made, the difference is ostensibly less important. For example, in the icefish case, if individual paired *t*-tests were performed to compare rest with activity at 8°C only, it would yield essentially the same, highly significant change ($P<0.01$) for both resistance and conductance. However, we argue that this would not be the immediate, or most appropriate, choice for the original two-factor (temperature and exercise) analysis. Furthermore, this would not circumvent the issue that the numerical change in resistance outwardly appears dramatically attenuated at 8°C in comparison with that at lower temperatures (Fig. 2B).

It is commonplace to represent changes in resistance or flow in relative terms (e.g. percentage change), especially when blood flow is measured in arbitrary units (i.e. by Doppler crystals without calibration). However, when discussed in relation to the change in flow, it is inappropriate to calculate a percentage change in a variable that changes non-linearly (Lautt, 1989). Thus, even in pairwise analysis, it is recommended that conductance is employed when flow changes more than pressure.

We caution that each experiment or dataset requires its own consideration. If the endpoint variable is blood flow or oxygen delivery, as we have primarily considered herein, conductance is the best choice for use in linear statistics. When both blood flow and pressure change in synchrony, it might be immaterial which is selected. However, in more-sophisticated analyses when the changes in resistance or conductance are compared between

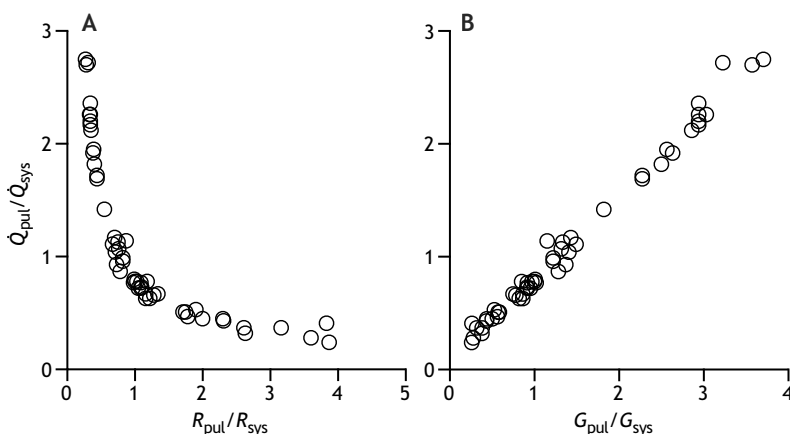


Fig. 4. Relationship between the ratio of pulmonary to systemic vascular resistance or conductance and shunt blood-flow ratio in turtles. Data are from Crossley et al. (1998). \dot{Q}_{pul} , pulmonary blood flow; \dot{Q}_{sys} , systemic blood flow; R_{pul} , pulmonary resistance; R_{sys} , systemic resistance; G_{pul} , pulmonary conductance; G_{sys} , systemic conductance. (A) The curvilinear relationship between R_{pul}/R_{sys} and $\dot{Q}_{pul}/\dot{Q}_{sys}$. (B) The linear relationship between G_{pul}/G_{sys} and $\dot{Q}_{pul}/\dot{Q}_{sys}$.

conditions (e.g. temperature) or species, the inappropriate selection can lead to erroneous conclusions. The choice should be made on a case-by-case basis and, in some circumstances, it may be most appropriate to report changes in both conductance and resistance.

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Competing interests

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