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Effect of intestinal pressure on fistula closure during vacuum assisted treatment: A computational approach

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ABSTRACT

Background: Enterocutaneous fistulae, pathological communications between the intestinal lumen and the abdominal skin, can arise as serious complication of gastrointestinal surgery. A current non-surgical treatment for this pathology involves topical application of sub-atmospheric pressure, also known as vacuum assisted closure (VAC). While this technique appears to be promising, surgeons report a number of cases in which its application fails to achieve fistula closure. Here, we evaluate the fistula's physical properties during the vacuum assisted closure process in a computational approach exploring the relevance of intraluminal intestinal pressure.

Methods: A mathematical model formulated by differential equations based on tissue elasticity properties and principles of fluid mechanics was created and forcing functions were integrated to mimic intestinal pressure dynamics. A software to solve equations and to fit the model to experimentally obtained data was developed. This enabled simulations of vacuum assisted fistula closure under different intestinal pressure.

Results: The simulation output indicates conditions, in which fistula closure can or cannot be expected suggesting favoured or impeded healing, respectively. When modifications of intestinal pressure, as observed in fistula accompanying pathologies, are integrated, the outcome of fistula closure changes considerably. Rise of intestinal pressure is associated with delay of fistula closure and temporary fistula radius augmentation, while reduction of intestinal pressure during sub-atmospheric pressure treatment contributes to a faster and direct fistula closure.

Conclusion: From the model predictions, we conclude that administration of intestinal pressure decreasing compounds (e.g. butylscopolamine, glucagon) may improve VAC treatment, while intestinal pressure increasing drugs should be avoided.

1. Introduction

Enterocutaneous fistulae (ECF) represent one of the most apprehensive complications of gastrointestinal surgery. This pathology is significant in terms of the high health risk it implies and the elevated economic cost it entails to the health care system.[1] Chapman and co-workers[2] rose the awareness that in the majority of cases the basis of ECF treatment should be, preferably, of conservative nature and emphasized the importance of nutritional and sepsis control. Though fistulae management experienced progress, treatment remained unsatisfactory calling for new therapeutic strategies. In 1992 Fernández and co-workers designed a vacuum-compaction device that applies sub-atmospheric pressure at the external extreme of the enterocutaneous fistula to achieve its closure.[3] This therapeutic approach, also referred to as vacuum assisted closure (VAC), has been implemented in 91 patients during the last years with promising results.[4] Under sub-atmospheric conditions, enterocutaneous fistula showed a reduced output and spontaneous closure was attained for a high percentage of patients. Recently, we successfully developed the first

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deterministic mathematical model to describe the closing mechanism of fistula under vacuum assistance.[5] The model assumed the fistula as a flexible tube with a Newtonian fluid circulating inside under a laminar regime and the intestine having constant atmospheric pressure during the treatment.

While in physiological state the average intraluminal pressure has been shown to be close to atmospheric pressure, forces vary under pathological conditions.[6–10] Patients presenting ECF are often in circumstances that are associated with high intestinal pressures. Intraluminal pressures may be increased due to various reasons including postoperative increased bowel wall tension, persisting bowel obstruction, stasis, bacterial overgrowth and malfunctioning of the ileocecal valve.[11,12] In a number of patients the fistula is complicated by inflammatory bowel syndrome. Under these circumstances the bowel smooth muscle may show higher intraluminal pressures.[13,14] There is a 25% failure of ECF closing using VAC treatment and the aforementioned conditions have been described as possible hindrance factors.[15] In this light, it appears relevant to study the influence of intestinal pressure on the outcome of ECF treatment using vacuum assistance. We performed computational simulations and developed a mathematical model comprising different functions describing intestinal pressure dynamics.

The obtained results suggest that during sub-atmospheric pressure treatment, increments in intestinal pressure may hinder or even preclude fistula closure, whereas a diminution of intestinal pressure may accelerate the closing process and facilitate the preservation of tissue integrity.

2. Vacuum applying methodology

Enterocutaneous fistulae are pathological communications between the lumen of the intestine and the external abdominal skin (Fig. 1). The objective of the VAC methodology is to achieve fistula closure without surgery and without immobilizing the patient. After cleaning the patient's abdominal skin, the surgeon describes a circular area from the abdominal extreme of the enterocutaneous fistula with Karaya paste (a biological adhesive for skin protection).[4] A polymeric foam is placed on this circular area, which is then covered by a low-density, highly malleable polythene film (18–21 μm) constituting the compaction chamber. A catheter, long enough to allow the patient to move, connects this chamber to a vacuum pump. When the pump is turned on, vacuum is applied. The compaction chamber volume decreases and the fistula can achieve its transitory closure. Depending on the evolution, this closure may be permanent.

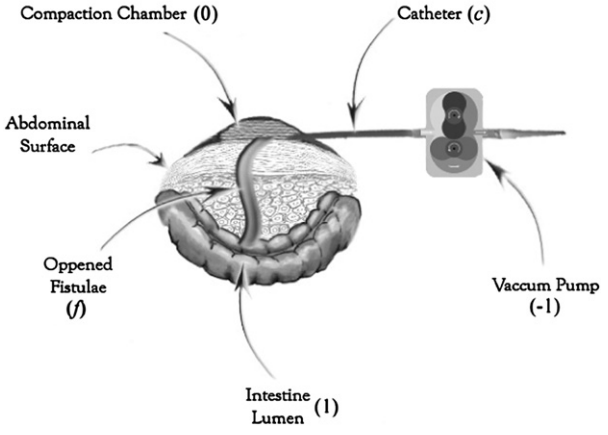

Fig. 1. Scheme of the computational model. The schematic representation depicts the intestine (1) connected to the compaction chamber (0) by the fistula (f). The compaction chamber in turn is connected to the vacuum pump (-1) by the catheter (c). An equivalent volume flux enters and leaves the fistula, the compaction chamber and the catheter connected to the vacuum pump.

3. Computational model incorporating intestinal pressure dynamics

In order to simulate the behaviour of the fistula during VAC application and evaluate the effect of intestinal pressure on the efficacy of this treatment, a model of five serial compartments was developed (Fig. 1). A complete description of the employed assumptions and equations can be found in the Supplementary information section. Briefly summarized, the fistula is simulated as a flexible cylinder of constant length (L_f) and variable radius as function of time ($r_f(t)$) with an incompressible fluid circulating through the fistula, once the vacuum pump is turned on. The flux through the system, described by the Poiseuille law, is conserved. The negative pressure generated by the vacuum pump (P_{-1}) follows an exponential decay kinetics.[5] The fistula radius depends on the pressure at the middle part of the fistula (P_f) and the inverse of fistula compressibility (D_f). The fistula extreme communicating with the intestine is exposed to the intestinal pressure which is a function of time ($P_1(t)$). Following these assumptions a computational model, describing the behaviour of the fistula radius during VAC as a function of time, was developed. This model is determined by the following expression which relates the rate of fistula radius change ($\dot{r}_f$) with the radius of fistula (r_f):

$$\dot{r}_f = \frac{a_6 r_f^6 + a_4 r_f^4 + a_0}{a_1 r_f} \tag{1}$$

where a_6, a_4, a_1 and a_0 depend on the physical properties of fistula, intestine and vacuum system and are given by:

$$a_6 = -\frac{\pi^2 D_f}{4\eta} \tag{2}$$

$$a_4 = \frac{\pi(P_1 - P_a)}{8 L_f \eta} + \frac{\pi^2 D_f r_0}{4\eta} \tag{3}$$

$$a_0 = -Q_B - \frac{\dot{P}_1}{D_0} \tag{4}$$

$$a_1 = L_f \pi \left(1 + 4\frac{D_f}{D_0}\right) \tag{5}$$

where D_f, D_0, η, L_f, r_0, Q_B, P_a, P_1, $\dot{P}_1$ represent the inverse of fistula compressibility, the inverse of the compaction chamber compressibility, the fistulous fluid viscosity, the length of fistula, the initial fistula radius, the flux generated by the vacuum pump, the atmospheric pressure, the intestinal pressure, and the rate of intestinal pressure change, respectively.

At initial time ($t = 0$) the pressure within the system, which includes the intestine, fistula, compaction chamber and catheter connected to the vacuum pump, is assumed to be atmospheric (P_a). The effect of intestinal pressure on the fistula behaviour can be observed in the factors a_4 and a_0. The influence of intestinal pressure (P_1) and the rate of change of intestinal pressure ($\dot{P}_1$) on the rate of change of the fistula radius ($\dot{r}_f$) are reflected in expressions (3) and (4).

The behaviour of the model represented by Eqs. (1–5) is directly related to the intestinal pressure through expressions a_0 and a_4. The

intestinal pressure reflects several physiological processes which take place simultaneously and follow diverse patterns. In order to characterize its behaviour, the functional time dependence of the intestinal pressure needs to be identified. As a first approach we tested several forcing functions (Table 1) of empirical nature (see Simulated Results and Discussion sections), which mimic the time evolution of intestinal pressure. In addition we used previously reported data on the pressure values which prevail inside the catheter connected to the vacuum pump in patients with ECF[5] to validate our model. The pressure in the catheter was calculated in our model by the following expression:

$$P_{-1} = f_1 + f_2 r_f^2 \tag{6}$$

where:

$$f_1 = 2P_a - P_1 + 2\pi L_f D_f r_0^2 - \frac{Q_B 8 L_c \eta}{\pi r_c^4} \tag{7}$$

$$f_2 = 2\pi L_f D_f \tag{8}$$

f_1 and f_2 show, similarly to what was previously described for the fistula radius, the role and physical effect of the different components of the model (fistula, intestine, compaction chamber and vacuum pump) in the resulting pressure measured at the catheter connecting the compaction chamber and the vacuum pump.

4. Methods

To evaluate the effect of intestinal pressure dynamics over the efficacy of the VAC treatment for enterocutaneous fistula closure by mathematical modelling a software that uses algorithms coded in Visual Basic was developed. The program numerically solves the differential equations involved in each type of model and subsequently fits the simulations to the experimental data (software and source code available by request). In the algorithm the model is loaded with each forcing function describing the time course of intestinal pressure (Table 1). Simulations result in a prediction of the time course of fistula radius and the pressure of intestine, fistula, compaction chamber and catheter, once the pump is turned on. For these simulations Eq. (1) combined with Eqs. (2–5) were numerically integrated employing the Euler method. The integration step was set to 10^{-4} s, guaranteeing the accuracy and stability of the numerical method.

Two statements of empirically gained information were employed in order to validate the model: firstly, the evidence that ECF reaches transitory closure in a time scale lower than 50 s and secondly the previous experimental measurements of the pressure time course in the catheter connected to the vacuum pump (P_{-1} in the model).[5] Thus, in a first screening, the algorithm was set to distinguish between parameter values (α_i for each forcing function) closing the fistula or not during the studied time range ($t < 50$ s). Subsequently, we found the set of parameters for each forcing function that minimized the sum of squares (SS) of the residues between the experimental data of the pressure time course in the catheter connected to the vacuum pump and the data simulated by the model. We call the latter procedure model-dependent fit to emphasize the fact that during the fitting process the constraints imposed by the mathematical model were taken into account (See Supplementary information).

Table 1
Intestinal pressure behaviour during treatment: the forcing functions. Functions loaded in the mathematical model proposed in Eqs. (1–5) to describe the behaviour of enterocutaneous fistula during VAC treatment including intestinal pressure changes. Each function represents the time course of intestinal pressure (P_1). For all the equations, α_0 is the intestinal pressure just before the vacuum pump is turned on, while α_i (with $i \neq 0$) are fitted parameters.

Function	Expression
Constant	$P_1(t) = \alpha_1$
Linear	$P_1(t) = \alpha_1 t + \alpha_0$
Quadratic	$P_1(t) = \alpha_2 t^2 + \alpha_1 t + \alpha_0$
First exponential	$P_1(t) = \alpha_1 (e^{\alpha_2 t} - 1) + \alpha_0$
Second exponential	$P_1(t) = \alpha_1 (1 - e^{-\alpha_2 t}) + \alpha_0$
Sinusoidal	$P_1(t) = \alpha_2 \sin(2\pi\alpha_1 t) + \alpha_0$

Every forcing function defining the time course of intestinal pressure was studied varying its α_i parameters values from -10^{20} to 10^{20}, covering the regions reported as physiological values.

Once the system was completely characterized, simulations including a differential perturbation of intestinal pressure (ΔP) were done. In these simulations a constant ΔP was added to each simulated data point of intestinal pressure (P_1) obtained for a given forcing function (using the best fitting parameters found by model-dependent fitting), starting from 0.0001 s to the end of the experimental time (50 s). ΔP values were changed iteratively (generating positive or negative perturbations) throughout repeated simulations.

5. Model validation against experimental data

We simulated fistula evolution after vacuum application under different intestinal pressure regimes (linear, quadratic, sinusoidal and exponential forcing functions; see Table 1). The initial time for each simulation (i.e. $t = 0$ s) was associated with the turning-on of the pump. Initially, to characterize the system behaviour, we performed simulations using constant intestinal pressure values ($P_1(t)$) above and below atmospheric pressure (P_a) (data not shown). In the case where $P_1(t) = P_a$, transient fistula closure was attained recovering previously published results.[5] However, constant intestinal pressure values different from atmospheric pressure (above and below) did not allow transient fistula closure in the studied time frame (50 s).

To explore the parameters space (α_i) allowing fistula closure for each of the tested forcing functions, we defined an auxiliary variable, φ, which takes the value 1 when the fistula closes during the experimental time or 0 when the fistula remains open. Fig. 2A shows that only certain positive values for α_1 parameter allow fistula closure for the model loaded with the linear forcing function. Fig. 2B shows the parameters space (α_1–α_2) for the quadratic forcing function, indicating the cases in which the fistula closes ($\varphi = 1$) or not ($\varphi = 0$). Successful closure was obtained for α_1 depicting a range of $1–4 \times 10^3$ dyn cm^{-2} s^{-1} and α_2 being within -10^2 and 10^{-1} dyn cm^{-2} s^{-2}. When the sinusoidal function was studied (Fig. 2C), cases of fistula closure were observed for α_1 and α_2 in the range of 1×10^{-3}–7×10^{-2} s^{-1} and 10^4–5.9×10^5 dyn cm^{-2}, respectively. Studies of the first exponential and second exponential forcing functions did not yield closure results (data not shown).

Once regions of the space parameters for the model loaded with each forcing function that allowed fistula closure within 50 s were identified, we verified, by model-dependent fitting, whether the model in these regions was able to describe our previous experimental results considering the experimental time course of the pressure in the catheter connected to the vacuum pump (P_{-1}). Fig. 3A displays the time course of the pressure near the pump for the model loaded with the assayed forcing functions. It can be observed that the sinusoidal function was not able to reproduce the experimental data within the studied time range. The linear forcing function departs from the experimental data at short times and only converges at long times. The quadratic forcing function however was capable to reproduce the entire pressure time course that was previously experimentally obtained.

To further analyse the model behaviour and the fistula closure mechanism, the pressure inside the fistula (P_f) and its radius (r_f) were monitored during each simulation. Regarding the time course of the fistula radius (Fig. 3B), the model loaded with both the linear and the sinusoidal forcing functions exhibits a transient radius increase followed by a decrease that ultimately ends in fistula closure within 10 s. On the contrary, the model loaded with the quadratic forcing function predicts that the radius falls in two regimes, slow at short times and faster at longer times. For the quadratic function fistula closure occurs ~16 s after the pump was turned on. Fig. 3C shows that the mean pressure inside the fistula increases during the first 5 s of treatment and rapidly decreases

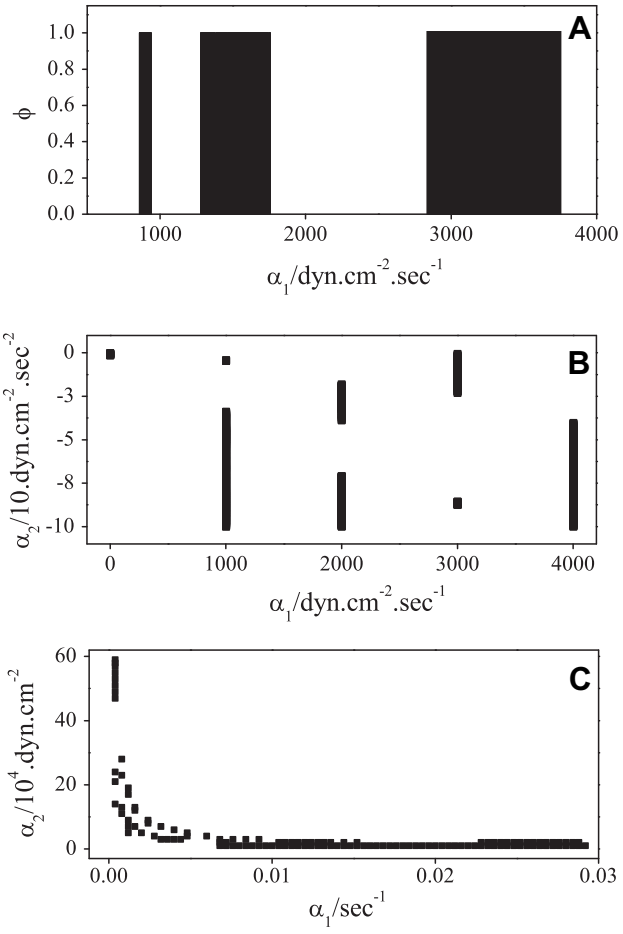

Fig. 2. Parameters space for successful fistula closure using different forcing functions. A. *Linear forcing function*: graph of the auxiliary variable φ vs. the α_1 parameter values tested in the different simulations. $\varphi = 1$ represents successful fistula closure and $\varphi = 0$ refers to the cases were the fistula remained open during the experimental time. B. and C. *Quadratic and Sinusoidal forcing functions respectively*: each black point of the graph ($\varphi = 1$) represents a case in which, for a given combination of α_1–α_2 parameters, the fistula closed during the experimental time. White areas of the graph represent unsuccessful cases ($\varphi = 0$).

below atmospheric values for both the linear and sinusoidal forcing functions simulations. In contrast, the pressure inside the fistula for the model loaded with the quadratic forcing function diminished homogeneously during the whole treatment until closure is achieved.

6. Results: model predictions regarding the effect of changes in intestinal pressure on fistula closure during sub-atmospheric pressure treatment

Our results indicate that the intestinal pressure dynamics described by a quadratic forcing function adequately reflected our previous experimental results. With this finding, we were able to examine the consequences of changes in intestinal pressure on the efficacy of VAC treatment for fistula closure. Simulations involving the quadratic function were repeated with addition of the constant perturbation of intestinal pressure (see Section 4, Methods). Fig. 4A shows the time course of fistula radius during treatment versus different pressure perturbations, either of positive or negative character (Fig. 4B). It can be observed that intestinal pressure shifts produces two opposing effects: increase of intestinal pressure values result in a transient enlargement of the fistula radius combined with a delay of the moment of fistula closure. On the contrary, at lower intestinal pressure values, there is no fistula radius enlargement and its closure is reached at a faster, nearly constant speed. Interestingly, the relationship of pressure changes over fistula closure time t_c (Fig. 4C) is asymmetric. Rising intestinal pressure provoked a t_c augmentation markedly higher than the t_c diminishment due to decrease of intestinal pressure. More specifically, slight diminutions of intestinal pressure lowered t_c by a factor of 2 whereas larger changes reached rapidly a minimal closure time of approximately 2 s. On the other hand, equivalent intestinal pressure augmentations increased t_c almost linearly rising the closure time up to 45 s. Positive pressure increments beyond the range, depicted on Fig. 4C, were not compatible with successful fistula closure during experimental time.

7. Discussion

Despite advances in nutritional care, infection control and surgical techniques, morbidity and mortality rates in patients suffering from enterocutaneous fistulae remain substantially high. While the global mortality rate of this pathology is between 15 and 37%, it drastically rises in cases of malnutrition and high-output and may exceed 75% when sepsis is concomitant.[16,17] Inflammatory bowel disease, diverticulitis, ischemic bowel and malignancy contribute and seem to portray classic barriers for fistula closure.[18] In patients with the latter concomitant conditions, VAC treatment

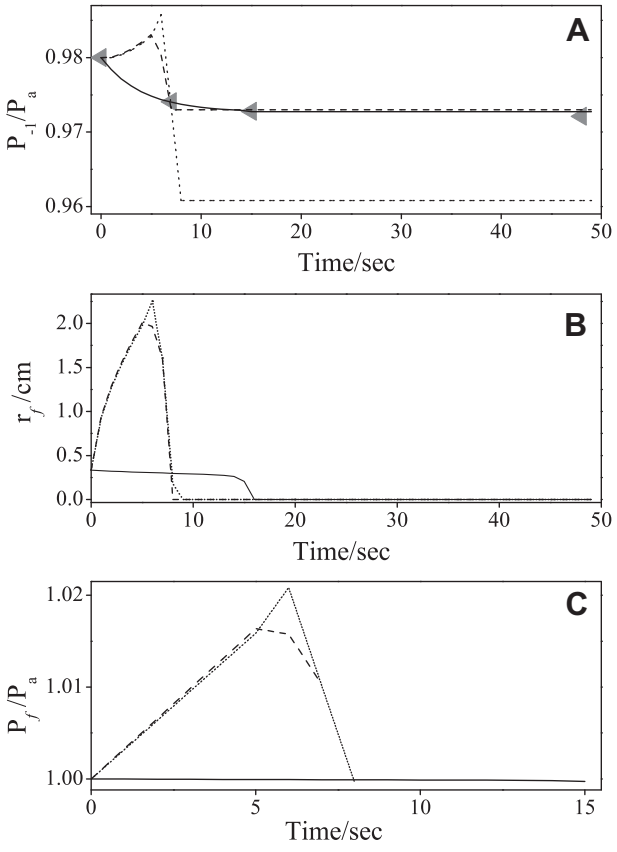

Fig. 3. Time course of vacuum pump pressure and fistula radius and mean pressure during treatment. A. Pressure in the catheter connected to the vacuum pump (P_{-1}) normalized by the atmospheric pressure (P_a) as a function of time. B. Simulated fistula radius (r_f) vs. time. C. Simulated mean pressure in the fistula (P_f) normalized by the atmospheric pressure (P_a) vs. time. Each curve corresponds to the model loaded with a different forcing function (linear (dashed line), quadratic (solid line) and sinusoidal (dotted line)) fitted to the experimental data (▲), $n = 15$ patients.[5]

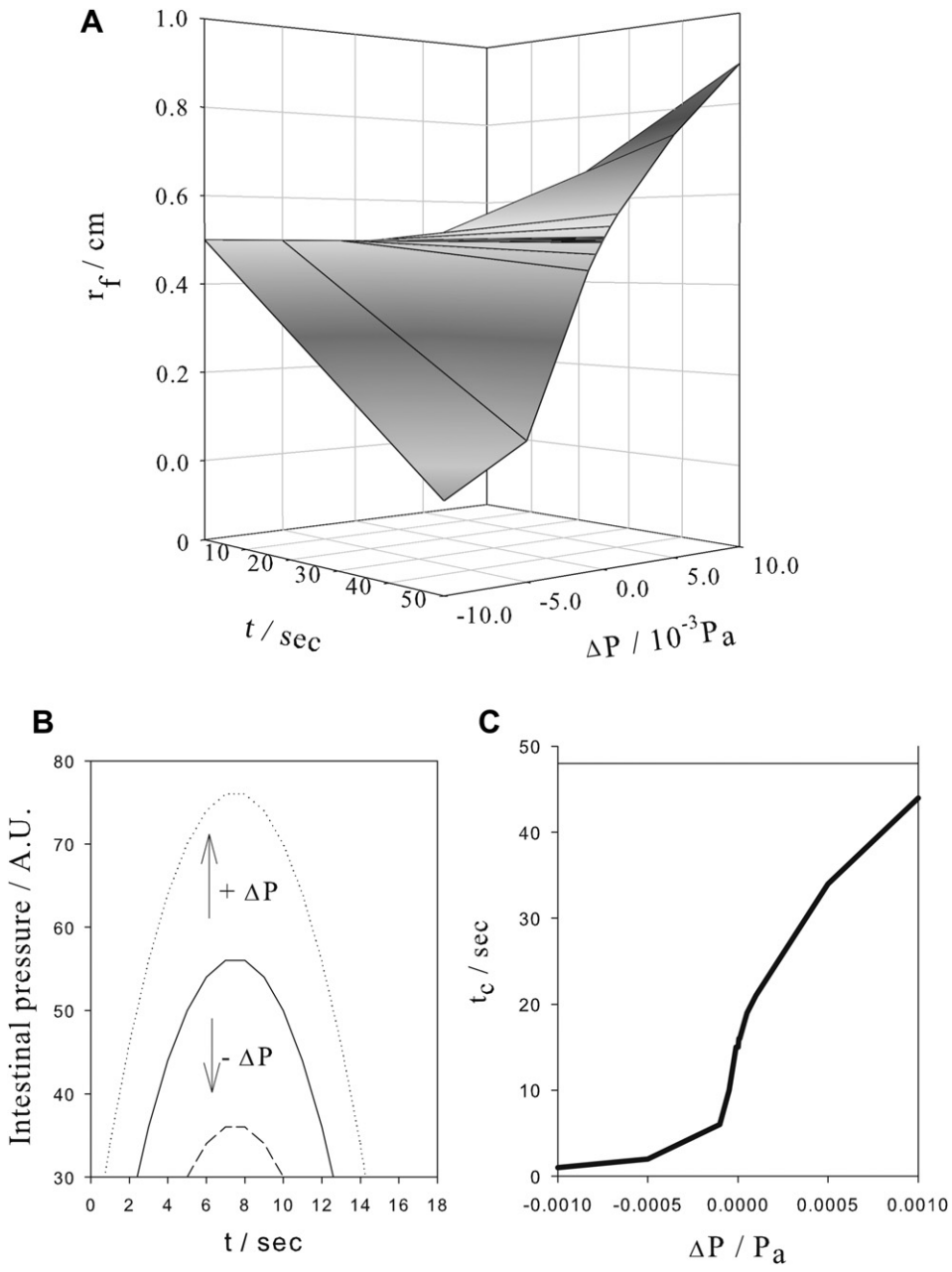

Fig. 4. Effect of intestinal pressure variations during VAC treatment. A. Prediction of the time course of fistula radius (r_f) at different values of constant perturbations in intestinal pressures (ΔP) normalized by the atmospheric pressure (P_a) during VAC treatment. B. Scheme representing the effect of perturbations on the intestinal pressure time evolution simulated by the quadratic forcing function. Positive ($+\Delta P$) and negative ($-\Delta P$) perturbations, correspond to an increase or decrease of the initial intestinal pressure (solid line). C. Fistula closure time (t_c) as a function of intestinal pressure perturbations. In the absence of intestinal pressure perturbations ($\Delta P/P_a = 0$) $t_c = 16$ s.

appears to be a good addition or even an alternative to reconstructive surgery.[19]

Mathematical models are commonly employed in biology[20] and medicine.[21] Its application has extended to study tumour growth,[22] haematopoiesis in haematological diseases[23] and myogenic response in reactive hyperaemia[24] among other pathologies. Here, we used a computational approach to investigate the influence of intestinal pressure changes on fistula closure behaviour during VAC treatment. It has been reported that intestinal pressure changes, both under physiological and pathological conditions.[6,7] However, to the authors' knowledge, there are no records of intestinal pressure measured during VAC treatment. Given the absence of clinical information, we simulated this pressure using forcing functions, a mathematical tool that has been previously applied in various complex biological problems.[25,26] We developed a mathematical model simulating non constant intestinal pressure by means of forcing functions. These functions can be regarded as the simplest expressions that gather the essential properties of intestinal pressure dynamics under physiological or pathological conditions. Accordingly, Eqs. (1–5) were loaded with forcing functions of increasing complexity: constant, linear, quadratic, and sinusoidal.

Best fitting results from simulations using the model loaded with linear and sinusoidal forcing functions depart from our previous experimental records (Fig. 3A). It can be observed that the fistula radius and mean pressure (Fig. 3B and C) show a sudden initial increment followed by a fast decrease. The quadratic forcing

function shows the best fitting results and accurately describes the experimental results during the entire studied time course (Fig. 3A). Furthermore it neither shows an augmentation of the fistula pressure nor the radius during the treatment. In contrast simulations involving the linear and sinusoidal functions drive to a non-physiological increase of the fistula radius (Fig. 3B). Thus the intestinal pressure behaviour during VAC treatment can be described using the quadratic function.

From experimental results obtained by Samson and co-workers,[8] the time derivative of intestinal pressure can be estimated 4.6×10^1 dyn cm^{-2} s^{-1}. Results of Quigley and co-workers[9] as well as Soffer and co-workers[7] show that the time derivative of intestinal pressure lies at 2.08×10^4 and 5.28×10^3 (dyn cm^{-2} s^{-1}), respectively. Our present simulations showed that α_1 parameter, a measure of the time derivative of the intestinal pressure, for the model loaded with quadratic functions (Fig. 2B) is in the range between 859–3748 and 1–4001 (dyn cm^{-2} s^{-1}). Thus, the here presented model allowed not only to simulate fistula closure behaviour under VAC, but also to predict intestinal pressure parameters in remarkable good agreement with the reported literature.

7.1. Is it possible to improve vacuum assisted closure of enterocutaneous fistulae by influencing intestinal pressure?

Our simulations demonstrate that intestinal pressure plays an important role on the behaviour of fistula closure during the application of sub-atmospheric pressure (Fig. 4). When applying disturbances (ΔP) to intestinal pressure simulations with the quadratic forcing function, the outcome changes considerably. While a rise of intestinal pressure is associated with a delay of fistula closure and temporary radius augmentation, the reduction of intestinal pressure during sub-atmospheric pressure treatment contributes to a much faster and direct fistula closure.

There are various pharmacological agents which exert different effects on digestive tract motility that are relevant in present clinical application. Having either prokinetic or spasmolytic effects, they modify intestinal motility and are used for the management of intestinal disorders and during diagnostic procedures.[27–30] According to our predictions, it seems favourable to lower the intestinal pressure prior to sub-atmospheric pressure treatment. Intestinal pressure and motor action are ensured by means of musculature as myoelectrical activity by the intrinsic nervous system, humoral factors and blood supply.[31] Spasmolytic agents such as butylscopolamine and glucagon are widely used in gastrointestinal radiology and endoscopy. Butylscopolamine, an anticholinergic agent, induces hypotonia by action on the post-ganglionic parasympathetic receptors in smooth muscles.[32] Also glucagon, a naturally occurring polypeptide hormone, reduces intestinal motility by acting on the smooth muscle of the bowel wall, yet its effectiveness is location-depended, being most effective in the duodenum and least effective in the colon.[33,34] Although these pharmacological agents have not been evaluated for their possible therapeutic use in fistula treatment so far, their role in the effectiveness of VAC treatment could be relevant. Future medical trials which evaluate the efficacy and systemic effects during their long-term use would be necessary.

8. Conclusions

Our computational model including forcing functions to mimic intestinal pressure temporal dynamics, suggests that intestinal pressure plays an important role during vacuum assisted treatment of enterocutaneous fistulae. Interestingly, our simulation findings showed that during VAC treatment low intestinal pressure represents a favourable determinant in the fistula closure process while, vice versa, high intestinal pressure notably opposes the conditions needed to achieve fistula closure.

From model predictions, we conclude that previous administration of compounds known to decrease intestinal pressure (such as butylscopolamine or glucagon) is worth considering in patients that suffer enterocutaneous fistulae and that undergo VAC treatment. A pharmacological pre-treatment could be even more convenient in patients in whom the fistula's underlying pathology causes elevated intestinal pressure and VAC treatment resulted unsuccessful.

Conversely, it can be reasoned that use of intestinal pressure increasing drugs could not be convenient. The mathematical model presented here validated with clinical data, allowed the study of fistula behaviour undergoing VAC treatment. Predictions suggest that intestinal pressure is of significant value in the treatment setting and makes further clinical-translated research in this surgical subject promising.

Ethical approval

None.

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Conflicts of interest

None.

Author contribution

D.I. Cattoni: data analysis, data interpretation and writing.
C. Ravazzola: acquisition of data and data analysis.
V. Tüngler: study design, data interpretation and writing.
D.E. Wainstein: study design, writing.
O. Chara: study supervision, study design, data interpretation and writing.

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Appendix. Supplementary information

Supplementary data related to this article can be found online at doi:10.1016/j.ijsu.2011.09.001.

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